TOXICOLOGICAL PROFILE FOR ETHYLBENZENE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

A Toxicological Profile for Ethylbenzene was released in September 1997. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

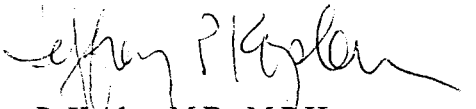
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure,* by *type of health efect* (death, systemic, immunologic, reproductive), and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 2.6 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.7 Biomarkers of Exposure and Effect
Section 2.10 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-888-42-ATSDR or 404-639-6357 ***Fax:*** 404-639-6359
E-mail: atsdric@cdc.gov ***Internet:*** http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History-The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume *III-Medical Management Guidelines for Acute Chemical Exposures*-is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29,4770 Buford Highway, NE, Atlanta, GA 30341-3724 •Phone: 770-488-7000 •FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 •Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 •Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 •Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #5 13, Washington, DC 20005 l Phone: 202-347-4976 l FAX: 202-347-4950 • e-mail: aoec@de;s.dgsvs.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-228-6850 •FAX: 847-228-1856.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1 . Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2 . Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for ethylbenzene. The panel consisted of the following members:

1. Dr. G.A. Shakeel Ansari, Professor, Department of Human Biological Chemistry and Genetics and Pathology, University of Texas Medical Branch, 301 University Boulevard, 5 14 Basic Science Building, Galveston, Texas;

2. Dr. R. Ryan DuPont, Professor, Utah State University, Utah Water Research Laboratory, UMC-8200, Logan, Utah; and

3. Edwin Kinkead, Private Consultant, 25973 Walnut Ct., Bonita Springs, Florida.

These experts collectively have knowledge of ethylbenzene's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about ethylbenzene and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Ethylbenzene has been found in at least 720 of the 1,467 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which ethylbenzene is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact.

If you are exposed to ethylbenzene, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS ETHYLBENZENE?

Ethylbenzene is a colorless liquid that smells like gasoline. You can smell ethylbenzene in the air at concentrations as low as 2 parts of ethylbenzene per million parts of air by volume (ppm). It evaporates at room temperature and burns easily. Ethylbenzene occurs naturally in coal tar and petroleum. It is also found in many products, including paints, inks, and insecticides. Gasoline contains about 2% (by weight) ethylbenzene. Ethylbenzene is used primarily in the production of styrene. It is also used as a solvent, a component of asphalt and naphtha, and in fuels. In the

chemical industry, it is used in the manufacture of acetophenone, cellulose acetate, diethylbenzene, ethyl anthraquinone, ethylbenzene sulfonic acids, propylene oxide, and α-methylbenzyl alcohol. Consumer products containing ethylbenzene include pesticides, carpet glues, varnishes and paints, and tobacco products. In 1994, approximately 12 billion pounds of ethylbenzene were produced in the United States. For more information on the physical and chemical properties of ethylbenzene, and its production, disposal, and use, see Chapters 3 and 4.

1.2 WHAT HAPPENS TO ETHYLBENZENE WHEN IT ENTERS THE ENVIRONMENT?

Ethylbenzene is most commonly found as a vapor in the air. This is because ethylbenzene moves easily into the air from water and soil. Once in the air, other chemicals help break down ethylbenzene into chemicals found in smog. This breakdown happens in less than 3 days with the aid of sunlight. In surface water such as rivers and harbors, ethylbenzene breaks down by reacting with other compounds naturally present in the water. In soil, the majority of ethylbenzene is broken down by soil bacteria. Since ethylbenzene binds only moderately to soil, it can also move downward through soil to contaminate groundwater. Near hazardous waste sites, the levels of ethylbenzene in the air, water, and soil could be much higher than in other areas. For more information on ethylbenzene in the environment, see Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO ETHYLBENZENE?

There are a variety of ways you may be exposed to this chemical. If you live in a highly populated area or near many factories or heavily traveled highways, you may be exposed to ethylbenzene in the air. Releases of ethylbenzene into these areas occur from burning oil, gas, and coal and from discharges of ethylbenzene from some types of factories. The median level of ethylbenzene in city and suburban air is about 0.62 parts of ethylbenzene per billion parts (ppb) of air. In contrast, the median level of ethylbenzene measured in air in country locations is about 0.01 ppb. Indoor air has a higher median concentration of ethylbenzene (about 1 ppb) than outdoor air. This is

because ethylbenzene builds up after you use household products such as cleaning products or paints.

Ethylbenzene was found in only one of ten U.S. rivers and streams tested in 1982 and 1983. The average level measured was less than 5.0 ppb. Ethylbenzene gets into water from factory releases, boat fuel, and poor disposal of waste. Background levels in soils have not been reported. Ethylbenzene may get into the soil by gasoline or other fuel spills and poor disposal of industrial and household wastes.

Some people are exposed to ethylbenzene in the workplace. Gas and oil workers may be exposed to ethylbenzene either through skin contact or by breathing ethylbenzene vapors. Varnish workers, spray painters, and people involved in gluing operations may also be exposed to high levels of ethylbenzene. Exposure may also occur in factories that use ethylbenzene to produce other chemicals.

You may be exposed to ethylbenzene if you live near hazardous waste sites containing ethylbenzene or areas where ethylbenzene spills have occurred. Higher-than-background levels of ethylbenzene were detected in groundwater near a landfill and near an area where a fuel spill had occurred. No specific information on human exposure to ethylbenzene near hazardous waste sites is available.

You may also be exposed to ethylbenzene from the use of many consumer products. Gasoline is a common source of ethylbenzene exposure. Other sources of ethylbenzene exposure come from the use of this chemical as a solvent in pesticides, carpet glues, varnishes and paints, and from the use of tobacco products. Ethylbenzene does not generally build up in food. However, some vegetables may contain very small amounts of it. For more information on human exposure to ethylbenzene, see Chapter 5.

1.4 HOW CAN ETHYLBENZENE ENTER AND LEAVE MY BODY?

When you breathe air containing ethylbenzene vapor, it enters your body rapidly and almost completely through your lungs. Ethylbenzene in food or water can also rapidly and almost completely enter your body through the digestive tract. It may enter through your skin when you come into contact with liquids containing ethylbenzene. Ethylbenzene vapors do not enter through your skin to any large degree. People living in urban areas or in areas near hazardous waste sites may be exposed by breathing air or by drinking water contaminated with ethylbenzene.

Once in your body, ethylbenzene is broken down into other chemicals. Most of it leaves in the urine within 2 days. Small amounts can also leave through the lungs and in feces. Liquid ethylbenzene that enters through your skin is also broken down. Ethylbenzene in high levels is broken down slower in your body than low levels of ethylbenzene. Similarly, ethylbenzene mixed with other solvents is also broken down more slowly than ethylbenzene alone. This slower breakdown will increase the time it takes for ethylbenzene to leave your body. For more information on how ethylbenzene enters and leaves the body, see Chapter 2.

1.5 HOW CAN ETHYLBENZENE AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

1. PUBLIC HEALTH STATEMENT

At certain levels, exposure to ethylbenzene can harm your health. People exposed to high levels of ethylbenzene in the air for short periods have complained of eye and throat irritation. Persons exposed to higher levels have shown signs of more severe effects such as decreased movement and dizziness. No studies have reported death in humans following exposure to ethylbenzene alone. However, evidence from animal studies suggests that it can cause death at very high concentrations in the air (about 2 million times the usual level in urban air). Whether or not longterm exposure to ethylbenzene affects human health is not known because little information is available. Short-term exposure of laboratory animals to high concentrations of ethylbenzene in air may cause liver and kidney damage, nervous system changes, and blood changes. The link between these health effects and exposure to ethylbenzene is not clear because of conflicting results and weaknesses in many of the studies. Also, there is no clear evidence that the ability to get pregnant is affected by breathing air or drinking water containing ethylbenzene, or coming into direct contact with ethylbenzene through the skin. Two long-term studies in animals suggest that ethylbenzene may cause tumors. One study had many weaknesses, and no conclusions could be drawn about possible cancer effects in humans. The other, a recently completed study, was more convincing, and provided clear evidence that ethylbenzene causes cancer in one species after exposure in the air to concentrations greater than 740 ppm that were approximately 1 million times the levels found in urban air. At present, the federal government has not identified ethylbenzene as a chemical that may cause cancer in humans. However, this may change after consideration of the new data.

There are no reliable data on the effects in humans after eating or drinking ethylbenzene or following direct exposure to the skin. For this reason, levels of exposure that may affect your health after eating, drinking, or getting ethylbenzene on your skin are estimated from animal studies. There are only two reports of eye or skin exposure to ethylbenzene. In these studies, liquid ethylbenzene caused eye damage and skin irritation in rabbits. More animal studies are available that describe the effects of breathing air or drinking water containing ethylbenzene.

For more information on levels of exposure associated with harmful health effects, see Chapter 2. ETHYLBENZENE

1.6 HOW CAN ETHYLBENZENE AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

Since ethylbenzene is contained in many consumer products (including gasoline, paints, inks, pesticides, and carpet glue), it is possible for children to be exposed to ethylbenzene, especially by inhalation. Children might also be exposed to ethylbenzene from hazardous waste. Ethylbenzene vapors are heavier than air, and children generally'spend more time on the floor or ground than do adults. We do not know whether children would be different than adults in their weight-adjusted intake of ethylbenzene.

No data describe the effect of exposure to ethylbenzene on children or immature animals. It is likely that children would show the same health effects as adults. Respiratory and eye irritation and dizziness are the most prevalent signs of exposure to high levels of ethylbenzene in adults, and children would probably also exhibit these effects. We do not know whether children differ in their susceptibility to the effects of ethylbenzene. We do not know whether ethylbenzene causes birth defects in people. Minor birth defects have occurred in newborn animals whose mothers were exposed by breathing air contaminated with ethylbenzene.

We do not know whether ethylbenzene can cross the placenta to an unborn child or accumulate significantly in breast milk.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO ETHYLBENZENE?

If your doctor finds that you have been exposed to significant amounts of ethylbenzene, ask your doctor if children may also be exposed. When necessary your doctor may need to ask your state public heath department to investigate.

1. PUBLIC HEALTH STATEMENT

Ethylbenzene is found in consumer products including gasoline, pesticides, carpet glues, varnishes, paints, and tobacco products. Exposure to ethylbenzene vapors from household products and newly installed carpeting can be minimized by using adequate ventilation. Household chemicals should be stored out of reach of young children to prevent accidental poisonings. Always store household chemicals in their original labeled containers; never store household chemicals in containers children would find attractive to eat or drink from, such as old soda bottles. Gasoline should be stored in a gasoline can with a locked cap. Keep your Poison Control Center's number by the phone. To minimize exposure, children should be kept out of areas where products that contain ethylbenzene are being used. Sometimes older children sniff household chemicals in an attempt to get high. Your children may be exposed to ethylbenzene by inhaling products containing it, such as paints, varnishes, or gasoline. Talk with your children about the dangers of sniffing chemicals.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ETHYLBENZENE?

Ethylbenzene is found in the blood, urine, breath, and some body tissues of exposed people. Urine is most commonly tested to determine exposure to ethylbenzene. The test measures the presence of substances formed following an exposure to ethylbenzene. These substances are formed by the breakdown of ethylbenzene. You should have this test done within a few hours after exposure occurs because these substances leave the body very quickly. Although this test can prove your exposure to ethylbenzene, it cannot yet predict the kind of health effects that might develop from that exposure. For more information on the different substances formed by ethylbenzene breakdown and on tests to detect these substances in the body, see Chapters 2 and 6.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic

substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an S-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for ethylbenzene include the following:

The federal government has developed regulatory standards and guidelines to protect you from possible health effects of ethylbenzene in the environment. EPA's Office of Drinking Water (ODW) set 700 ppb (this equals 0.7 milligrams ethylbenzene per liter of water or mg/L) as the acceptable exposure concentration of ethylbenzene in drinking water for an average weight adult. This value is for lifetime exposure and is set at a level that is expected not to increase the chance of having (noncancer) adverse health effects. The same EPA office (ODW) set higher acceptable levels of ethylbenzene in water for shorter periods (20 ppm or 20 mg/L for 1 day, 3 ppm or 3 mg/L for 10 days). EPA has determined that exposures at or below these levels are acceptable for small children. If you eat fish and drink water from a body of water, the water should contain no more than 1.4 mg ethylbenzene per liter.

EPA requires that a release of 1,000 pounds or more of ethylbenzene be reported to the federal government's National Response Center in Washington, D.C.

OSHA set a legal limit of 100 ppm ethylbenzene in air. This is for exposure at work for 8 hours per day.

NIOSH also recommends an exposure limit for ethylbenzene of 100 ppm. This is for exposure to ethylbenzene in air at work for up to 10 hours per day in a 40-hour work week. NIOSH also set a limit of 125 ppm for a 15minute period.

For more information on regulations and advisories, see Chapter 7.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: l-888-42-ATSDR (l-888-422-8737)
Fax: (404) 639-6314 or 639-6324

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22 16 1
Phone: (800) 553-6847 or (703) 605-6000

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of ethylbenzene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure- inhalation, oral, and dermal; and then by health effect-death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observedadverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR belieyes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear.

LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of ethylbenzene are indicated in Table 2- 1 and Figure 2- 1.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for ethylbenzene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding lethality in humans following only inhalation exposure to ethylbenzene. Matsumoto et al. (1992) reported the case of a 44-year-old man was found unconscious in his gasoline vapor-filled car with his clothes wet with gasoline containing ethylbenzene among many other constituents. The patient emptied at least 18 L of gasoline into his car and was exposed to it for 10 hours more. He was diagnosed as suffering from chemical burns. He denied ingestion of gasoline, and no evidence of gasoline ingestion was found on examination. The patient died after 9 days of multiple organ failure. Ethylbenzene was detectable in his blood. However, it was not possible to determine the extent to which his death was due to exposure to ethylbenzene versus the other components of the gasoline.

The LC_{50} (lethal concentration, 50% kill) for rats following inhalation exposure to ethylbenzene is reported to be 4,000 ppm (Smyth et al. 1962) and 13,367 ppm (Ivanov 1962) following exposure durations of 4 and 2 hours, respectively. The doses required to cause 100% mortality in rats were shown to be 8,000 ppm (Smyth et al. 1962) and 16,698 ppm (Ivanov 1962) for 4- and 2-hour inhalation exposures, respectively. However, it is important to note that the results of both of these studies have limited utility because the recorded concentrations were not analytically verified. Although no studies were located regarding the effect of nutritional status on mortality, it has been postulated that food deprivation may decrease ethylbenzene toxicity since the detoxication of ethylbenzene is increased significantly in fasted rats (Nakajima and Sato 1979).

The lethality of ethylbenzene in animals following inhalation exposure has been shown to vary among species. This was demonstrated in a study using Fischer 344 rats, $B6C3F_1$ mice, and New Zealand White rabbits in which the animals were exposed to 0,400, 1,200, or 2,400 ppm ethylbenzene 6 hours a day for 4 days (Biodynamics 1986; Cragg et al. 1989). Mortality occurred in mice at half the dose (1,200 ppm) required to cause death in rats (2,400 ppm). All rabbits in each exposure group survived.

Wolf et al. (1956) evaluated the toxicity of ethylbenzene in Rhesus monkeys after inhalation exposure 7-8 hours a day, 5 days a week for 6 months. Two female Rhesus monkeys were exposed to 400 ppm ethylbenzene, and a male and female monkey were exposed to 600 ppm. No mortality was reported. Similarly, no mortality was reported by Wolf et al. (1956) in male and female rats (strain unspecified)

exposed to 0, 400, 600, or 1,250 ppm ethylbenzene, or male rats exposed to 2,200 ppm ethylbenzene in a similar study design. No mortality was observed in a 4-week inhalation study in which Fischer 344 rats and $B6C3F_1$ mice were exposed to 99,382, or 782 ppm ethylbenzene, 6 hours a day, 5 days a week; all New Zealand White rabbits survived after exposure to 1,610 ppm ethylbenzene in the same study (Cragg et al. 1989). In a 90-day study, no lethality was observed in Fischer 344/N rats and B6C3F1 mice exposed to 0,99,246,498,740, or 975 ppm ethylbenzene, 6 hours a day, 5 days a week (NTP 1992). Wolf et al. (1956) observed no mortality in male or female guinea pigs exposed to 0,400,600, or 1,250 (females only) ppm ethylbenzene; or rabbits exposed to 0,400, or 600 ppm (for males), or 0,400, 600, or 1,250 ppm (for females) ethylbenzene for 5 days a week, 7-8 hours a day for up to 6-7 months. Chronic-duration inhalation exposure of male and female Fischer 344 rats and $B6C3F_1$ mice to doses of 0,75,250, or 750 ppm for up to 2 years (103-104 weeks) revealed increased mortality (96% mortality) in male rats exposed to 750 ppm (NTP 1996). Male and female rats and mice in the other dose groups had mortality rates that did not differ significantly from the control group.

The LC_{50} values and all reliable LOAEL values for death in rats and mice following acute- or chronicduration exposure are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.2 Systemic Effects

Data are limited on the systemic effects of inhaled ethylbenzene in humans. Most of the information available is from case reports in which quantitative data on exposure concentrations and durations were not reported. In addition, most of these studies lack important study details or have confounding factors (e.g., simultaneous exposures to other toxic substances). In general, the systemic effects observed in humans were pulmonary and ocular irritation, and possible hematological alterations (Angerer and Wulf 1985; Cometto-Muniz and Cain 1995; Thienes and Haley 1972; Yant et al. 1930).

Several studies were located on the systemic effects of ethylbenzene in animals following inhalation exposure. The principal target organs appear to be the lungs, liver, and kidney, with transient toxic effects on the hematological system. However, no definitive conclusions can be drawn because of the limitations of many of the studies.

Table 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat (Fischer- 344)	4 d 6 hr/d				2400 M (100% mortality by day 3)	Biodynamics 1986; Cragg et al. 1989
2	Rat (NS)	4 hr				4000 M (LC_{50})	Smyth et al. 1962
3	Mouse (B6C3F1)	4 d 6 hr/d				1200 M (4/5 animals died by day 3)	Biodynamics 1986; Cragg et al. 1989
Systemic							
4	Rat (Fischer- 344)	4 d 6 hr/d	Resp	1200 M		2400 M (shallow breathing)	Biodynamics 1986; Cragg et al. 1989
			Hepatic		400M (increased liver weight)		
			Renal	400 M	1200M (increased relative kidney weight)		
			Ocular	400 M	1200M (lacrimation)		
			Bd Wt	1200 M			
			Other	400 M	1200M (yellow or brown anogenital staining)		

Table 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
5	Rat (Sprague-Dawley)	3 d 6 hr/d	Hepatic		2000M (increased liver-to-body weight ratio, increased cytochrome P-450 conc & increased NADPH-cytochrome C reductase activity; increased 7-ethyoxyresorufin, n-hexane hydroxylation & benz[a]pyrene)		Toftgard and Nilsen 1982
			Renal		2000M (increased kidney-to-body weight ratio & increased NADPH-cytochrome C reductase activity)		
6	Mouse (B6C3F1)	4 d 6 hr/d	Resp	400 M		1200 M (*shallow breathing*)	Biodynamics 1986; Cragg et al. 1989
			Hepatic	1200 M			
			Renal	1200 M			
			Ocular		400M (lacrimation)		
			Bd Wt	400 M			
7	Mouse (Swiss)	5 min	Resp		1432M (RD50; 50% respiratory depression due to sensory irritation)		De Ceaurriz et al. 1981
8	Mouse (Swiss-Webster)	30 min	Resp		4060M (50% respiratory depression)		Nielsen and Alarie 1982
9	Mouse (CFW)	20 min	Ocular		2000M (lacrimation & palpebral closure)		Tegeris and Balster 1994

Table 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
10	Rabbit (New Zealand)	4 d 6 hr/d	Resp	2400 M			Biodynamics 1986; Cragg et al. 1989
			Hepatic	2400 M			
			Renal	2400 M			
			Ocular		400 M (lacrimation)		
			Bd Wt	2400 M			
	Neurological						
11	Rat (Sprague-Dawley)	3 d 6 hr/d			2000 M (neurotransmission disturbance in the forebrain & hypothalmus)		Andersson et al. 1981
12	Rat (Fischer- 344)	4 d 6 hr/d		1200 M		2400 M (salivation, prostration)	Biodynamics 1986; Cragg et al. 1989
13	Rat (CFY)	4 hr		200 M	400 M (moderate activation in motor behavior)	2180 M (narcotic effects)	Molnar et al. 1986
14	Mouse (B6C3F1)	4 d 6 hr/d		400 M		1200 M (prostration & reduced activity)	Biodynamics 1986; Cragg et al. 1989
15	Mouse (CFW)	20 min			2000 M (posture changes, decreased arousal & rearing, disturbed gait, decreased mobility, righting reflex, decreased grip strength, increased landing foot splay, impaired psychomotor coordination)		Tegeris and Balster 1994

Table 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
16	Rabbit (New Zealand)	4 d 6 hr/d		2400 M			Biodynamics 1986; Cragg et al. 1989
17	Rabbit (New Zealand)	7 d 12 hr/d			750M (dopamine depletion)		Mutti et al. 1988
18	Rabbit (New Zealand)	7 d 12 hr/d			750M (dopamine depletion; HVA accumulation)		Romanelli et al. 1986
	Reproductive						
19	Rat (Fischer- 344)	4 d 6 hr/d		2400 M			Biodynamics 1986; Cragg et al. 1989
20	Rat (CFY)	Gd 7-15 24 hr/d				138 (resorptions)	Ungvary and Tatrai 1985
21	Mouse (B6C3F1)	4 d 6 hr/d		1200 M			Biodynamics 1986; Cragg et al. 1989
22	Mouse (CFLP)	Gd 6-15 24 hr/d		115 F			*Ungvary and* Tatrai 1985
23	Rabbit (New Zealand)	4 d 6 hr/d		2400 M			Biodynamics 1986; Cragg et al. 1989
24	Rabbit (New Zealand)	Gd 6-16 24 hr/d				230 F (abortions)	Ungvary and Tatrai 1985

Table 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Developmental							
25	Rat (CFY)	Gd 7-15 6 hr/d		138 F			Ungvary and Tatrai 1985
26	Rat (CFY)	Gd 7-15 24 hr/d				138 F (skeletal retardation & fetal resorptions)	Ungvary and Tatrai 1985
27	Mouse (CFLP)	Gd 6-15 24 hr/d				115 F (anomalies of uropoetic apparatus)	Ungvary and Tatrai 1985
28	Rabbit (New Zealand)	Gd 7-20 24 hr/d			115 F (decreased fetal weight)		Ungvary and Tatrai 1985
INTERMEDIATE EXPOSURE							
Systemic							
29	Rat (Wistar)	3 wk 5 d/wk 7 hr/d Gd 1-19 7 hr/d	Resp	985 F			Andrew et al. 1981
			Hepatic	97	959 F (increased liver weight)		
			Renal	97	959 F (increased kidney weight)		
			Bd Wt	985 F			
			Other	985 F			

Table 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
30	Rat (Fischer- 344)	4 wk 5 d/wk 6 hr/d	Resp	782			Cragg et al. 1989
			Cardio	782			
			Gastro	782			
			Hemato	382	782 (increased platelet counts in male; increased mean total leukocyte counts in male & females)		
			Musc/skel	782			
			Hepatic	382	782 (increased absolute & relative liver weight)		
			Renal	782			
			Endocr	782			
			Ocular	99	382 (sporadic incidence of lacrimation)		
			Bd Wt	782			
31	Rat (Wistar)	5-16 wk 5 d/wk 6 hr/d	Hepatic	300 M	600M (increased relative liver weight 10% at wk 9; increased microsomal protein content, NADPH -cytochrome C reductase activity, 7-ethoxy-coumarin O-diethylase & UDPG-transferase)		Elovaara et al. 1985
			Renal	300 M	600M (relative kidney weight increase 10% at wk 9)		
			Bd Wt	600			

Table 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
32	Rat (F344/N)	13 wk 5 d/wk 6 hr/d	Resp	740 M	975 M (increased relative lung weight)		NTP 1992
				99.4 F	246 F (increased absolute & relative lung weight)		
			Cardio	975			
			Gastro	975			
			Hemato	975			
			Musc/skel	975			
			Hepatic	99.4 M	246 M (increased absolute and relative liver weight)		
				246 F	498 F (increased absolute liver weight)		
			Renal	246 M	498 M (increased absolute & relative kidney weight		
				498 F	740 F <10%) (increased absolute *kidney weight <10%)*		
			Endocr	975			
			Ocular	975			
			Bd Wt	975			

Table 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
33	Mouse (B6C3F1)	4 wk 5 d/wk 6 hr/d	Resp	782			Cragg et al. 1989
			Cardio	782			
			Gastro	782			
			Hemato	782			
			Musc/skel	782			
			Hepatic	382	782 (increased mean absolute and relative liver weight)		
			Renal	782			
			Endocr	782			
			Ocular	782			
			Bd Wt	782			
34	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d	Resp	975			NTP 1992
			Cardio	975			
			Gastro	975			
			Hemato	975			
			Musc/skel	975			
			Hepatic	498 M	740 M (increased absolute and relative liver weight)		
				740 F	975 F (increased absolute & relative liver weight)		
			Renal	975 M			
				740 F	975 F (increased relative kidney weight)		
			Endocr	975			
			Ocular	975			
			Bd Wt	975			

Table 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
35	Rabbit (New Zealand)	Gd 1-24 7 d/wk 7 hr/d	Resp	962 F			Andrew et al. 1981
			Hepatic	99 F	962F (increased absolute & *relative liver weights in* pregnant rabbits)		
			Renal	962 F			
			Bd Wt	962 F			
			Other	962 F			
36	Rabbit (New Zealand)	4 wk 5 d/wk 6 hr/d	Resp	1610			Cragg et al. *1989*
			Cardio	1610			
			Gastro	1610			
			Hemato	1610			
			Musc/skel	1610			
			Hepatic	1610			
			Renal	1610			
			Endocr	1610			
			Ocular	1610			
			Bd Wt	1610			
Immunological/Lymphoreticular							
37	Rat (Wistar)	3 wk 5 d/wk 7 hr/d Gd 1-19 7 hr/d		97 F	959F (increased spleen weight)		Andrew et al. 1981
38	Rat (Fischer- 344)	4 wk 5 d/wk 6 hr/d		782			Cragg et al. 1989

Table 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
39	Rat (F344/N)	13 wk 5 d/wk 6 hr/d		975			NTP 1992
40	Mouse (B6C3F1)	4 wk 5 d/wk 6 hr/d		782			Cragg et al. 1989
41	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		975			NTP 1992
42	Rabbit (New Zealand)	4 wk 5 d/wk 6 hr/d		1610			Cragg et al. 1989
	Neurological						
43	Rat (Fischer- 344)	4 wk 5 d/wk 6 hr/d		99	382 (sporadic incidence of salivation)		Cragg et al. 1989
44	Rat (F344/N)	13 wk 5 d/wk 6 hr/d		975			NTP 1992
45	Mouse (B6C3F1)	4 wk 5 d/wk 6 hr/d		782			Cragg et al. 1989
46	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		975			NTP 1992
47	Rabbit (New Zealand)	4 wk 5 d/wk 6 hr/d		1610			Cragg et al. 1989

Table 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Reproductive							
48	Rat (Wistar)	3 wk 5 d/wk 7 hr/d Gd 1-19 7 hr/d		985 F			Andrew et al. 1981
49	Rat (Fischer- 344)	4 wk 5 d/wk 6 hr/d		782			Cragg et al. 1989
50	Rat (F344/N)	13 wk 5 d/wk 6 hr/d		975			NTP 1992
51	Mouse (B6C3F1)	4 wk 5 d/wk 6 hr/d		782			Cragg et al. 1989
52	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		975			NTP 1992
53	Rabbit (New Zealand)	Gd 1-24 7 d/wk 7 hr/d		962 F			Andrew et al. 1981
54	Rabbit (New Zealand)	4 wk 5 d/wk 6 hr/d		1610			Cragg et al. 1989

Table 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Developmental							
55	Rat (Wistar)	3 wk 5 d/wk 7 hr/d Gd 1-19 7 hr/d		97[b]	959 (skeletal anomalies, supernumerary ribs)		Andrew et al. 1981
56	Rabbit (New Zealand)	Gd 1-24 7 d/wk 7 hr/d		962			Andrew et al. 1981
CHRONIC EXPOSURE							
Death							
57	Rat (F344/N)	104 wk 5 d/wk 6 hr/d				750 M (2/50 survived)	NTP 1996
Systemic							
58	Rat (F344/N)	104 wk 5 d/wk 6 hr/d	Resp	750			NTP 1996
			Cardio	750			
			Gastro	750			
			Musc/skel	750			
			Hepatic	750			
			Renal	250	750 (renal tubule hyperplasia)		
			Endocr	750			
			Bd Wt	750			

Table 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
59	Mouse (B6C3F1)	103 wk 5 d/wk 6 hr/d	Resp	250 F	750M (alveolar epithelial metaplasia)		NTP 1996
			Cardio	750			
			Gastro	750			
			Musc/skel	750			
			Hepatic	250	750F (syncytial alteration, hypertrophy, necrosis, eosinophilic focus)		
			Renal	750			
			Endocr	250	750 (follicular cell hyperplasia in thyroid gland)		
			Bd Wt	750			
	Immunological/Lymphoreticular						
60	Rat (F344/N)	104 wk 5 d/wk 6 hr/d		750			*NTP 1996*
61	Mouse (B6C3F1)	103 wk 5 d/wk 6 hr/d		750			NTP 1996
	Neurological						
62	Rat (F344/N)	104 wk 5 d/wk 6 hr/d		750			NTP 1996
63	Mouse (B6C3F1)	103 wk 5 d/wk 6 hr/d		750			NTP 1996

Table 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Reproductive							
64	Rat (F344/N)	104 wk 5 d/wk 6 hr/d		250 M		750 M (interstitial cell adenoma, bilateral testicular adenoma)	NTP 1996
				750 F			
65	Mouse (B6C3F1)	103 wk 5 d/wk 6 hr/d		750			NTP 1996
Cancer							
66	Rat (F344/N)	104 wk 5 d/wk 6 hr/d				750 (CEL: renal tubule adenoma or carcinoma, M: 21/50, F: 8/49; males: 44/50 testicular adenoma)	NTP 1996
67	Mouse (B6C3F1)	103 wk 5 d/wk 6 hr/d				750 M CEL: alveolar/bronchiolar adenoma, 16/50, alveolar/bronchiolar adenoma or carcinoma, 19/50)	NTP 1996
						750 F (CEL: hepatocellular adenoma, 16/50; hepatocellular adenoma or carcinoma, 25/50)	

[a]The number corresponds to entries in Figure 2-1.

[b]Used to derive an intermediate inhalation MRL of 1.0 ppm. Concentration divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestational day; Hemato = hematological; hr = hour(s); HVA = homovanillic acid; LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; min = minute(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; RD_{50} = respiratory depression, 50%; Resp = respiratory; wk = week(s)

Figure 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation

Acute (≤14 days)

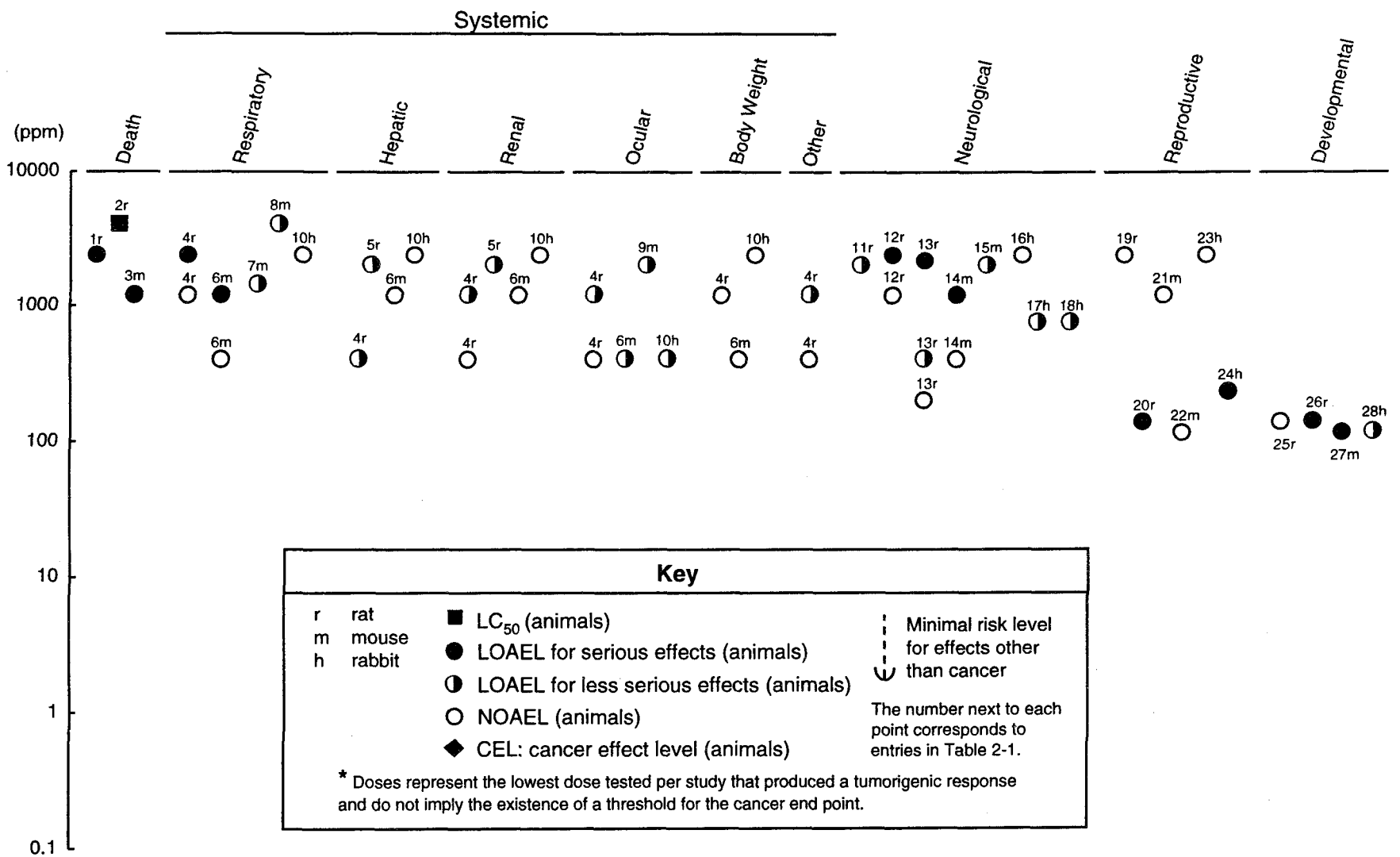


Figure 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (cont.)

Intermediate (15-364 days)

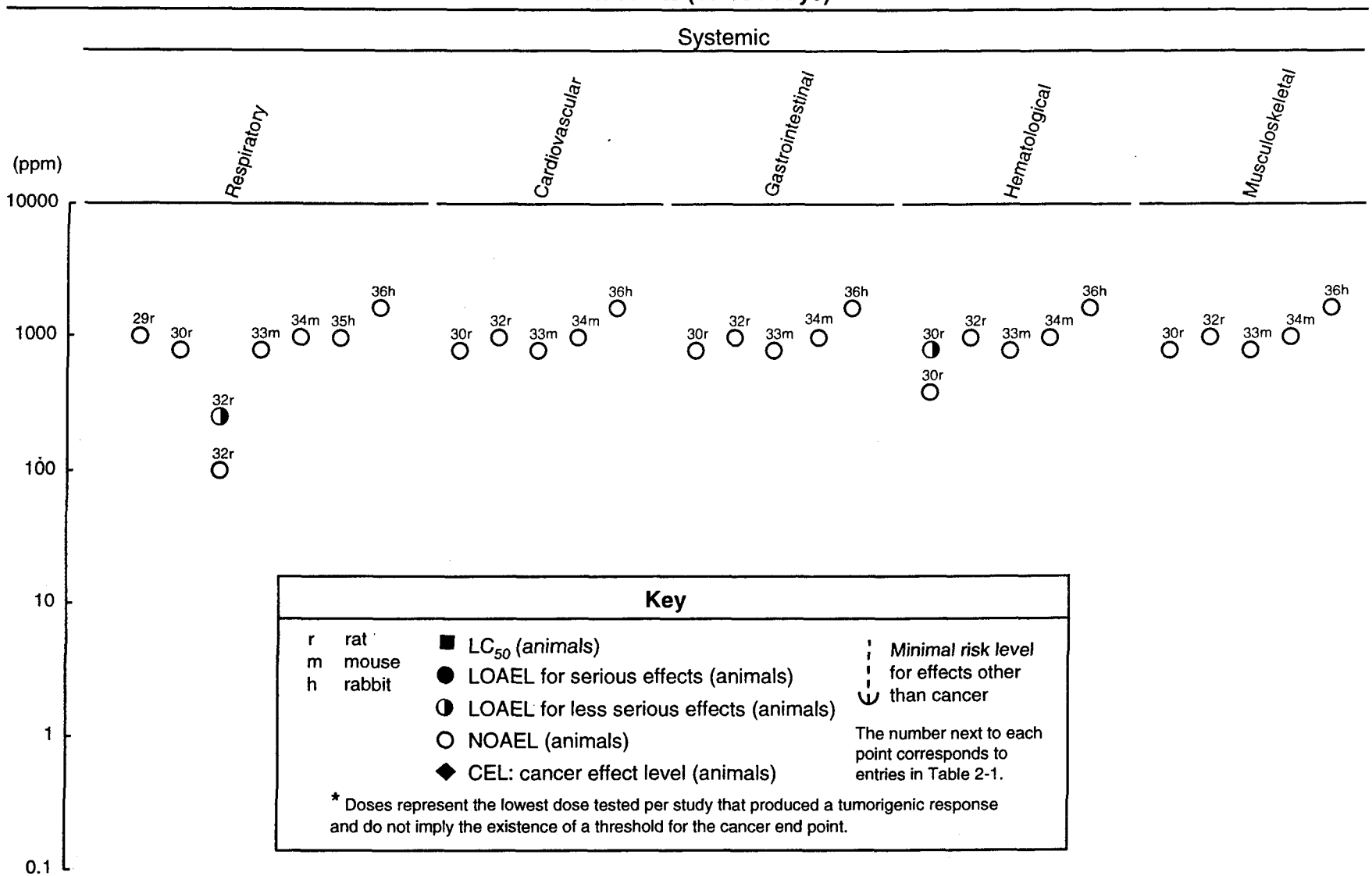


Figure 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (cont.)

Intermediate (15-364 days)

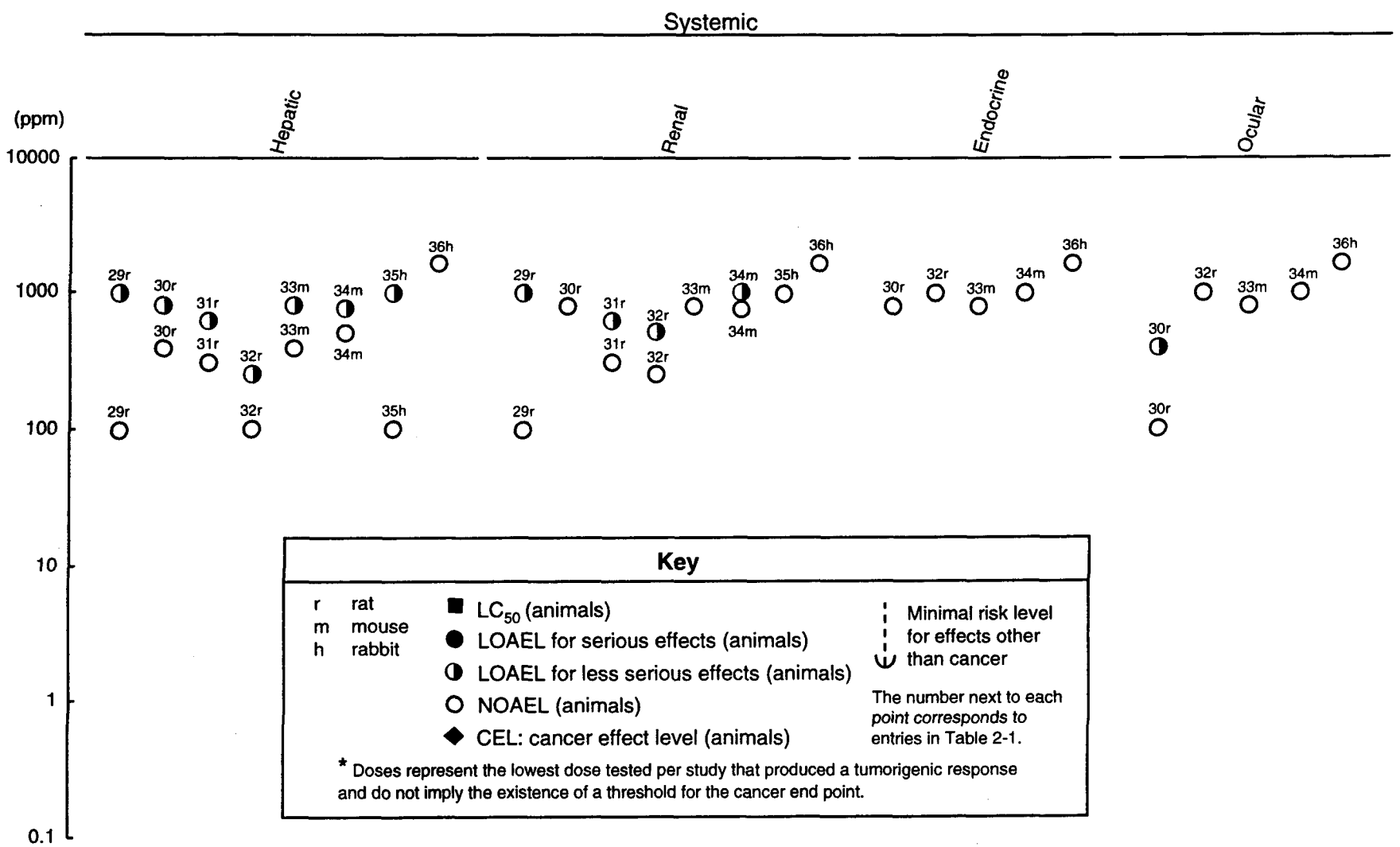


Figure 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (cont.)

Intermediate (15-364 days)

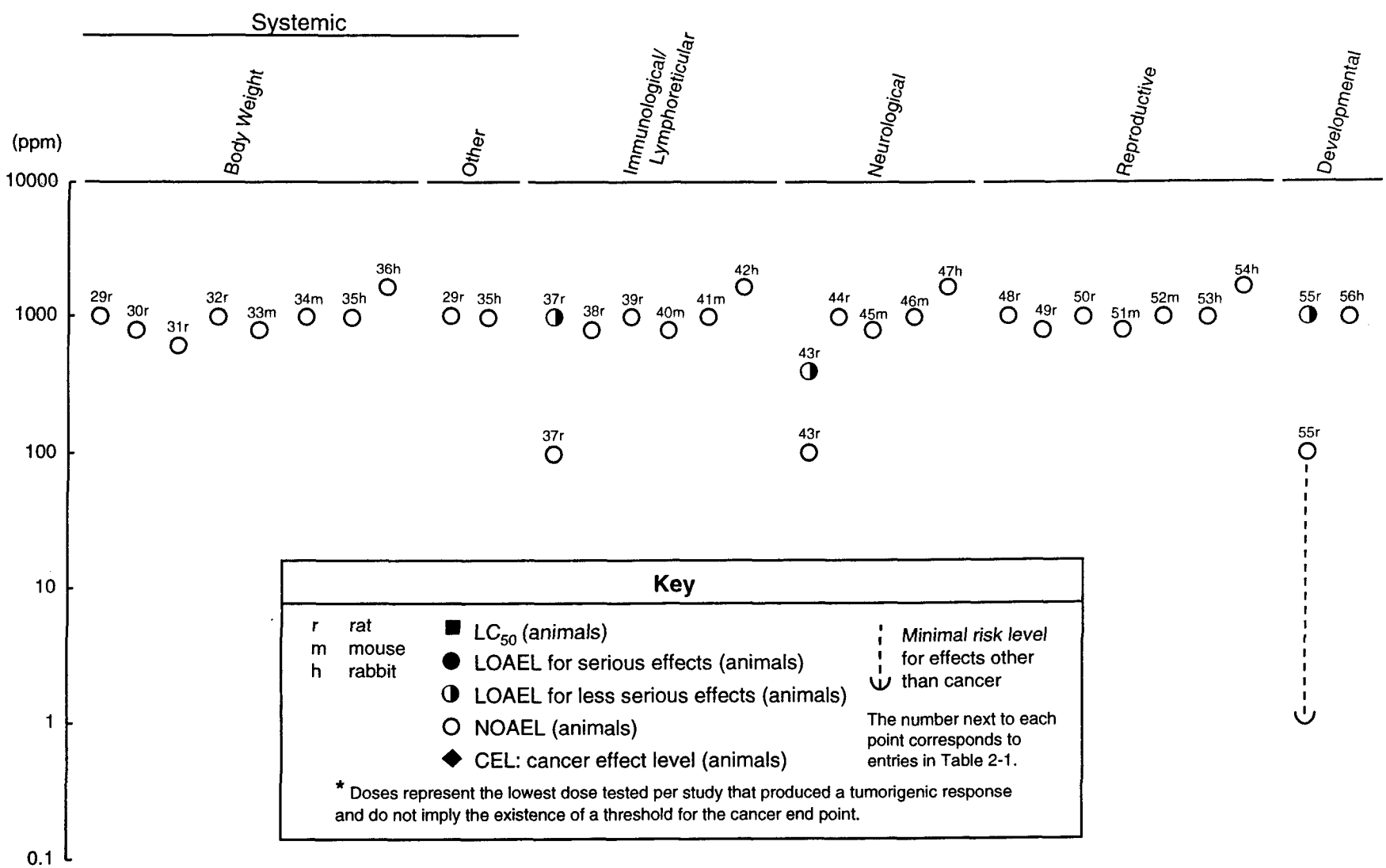
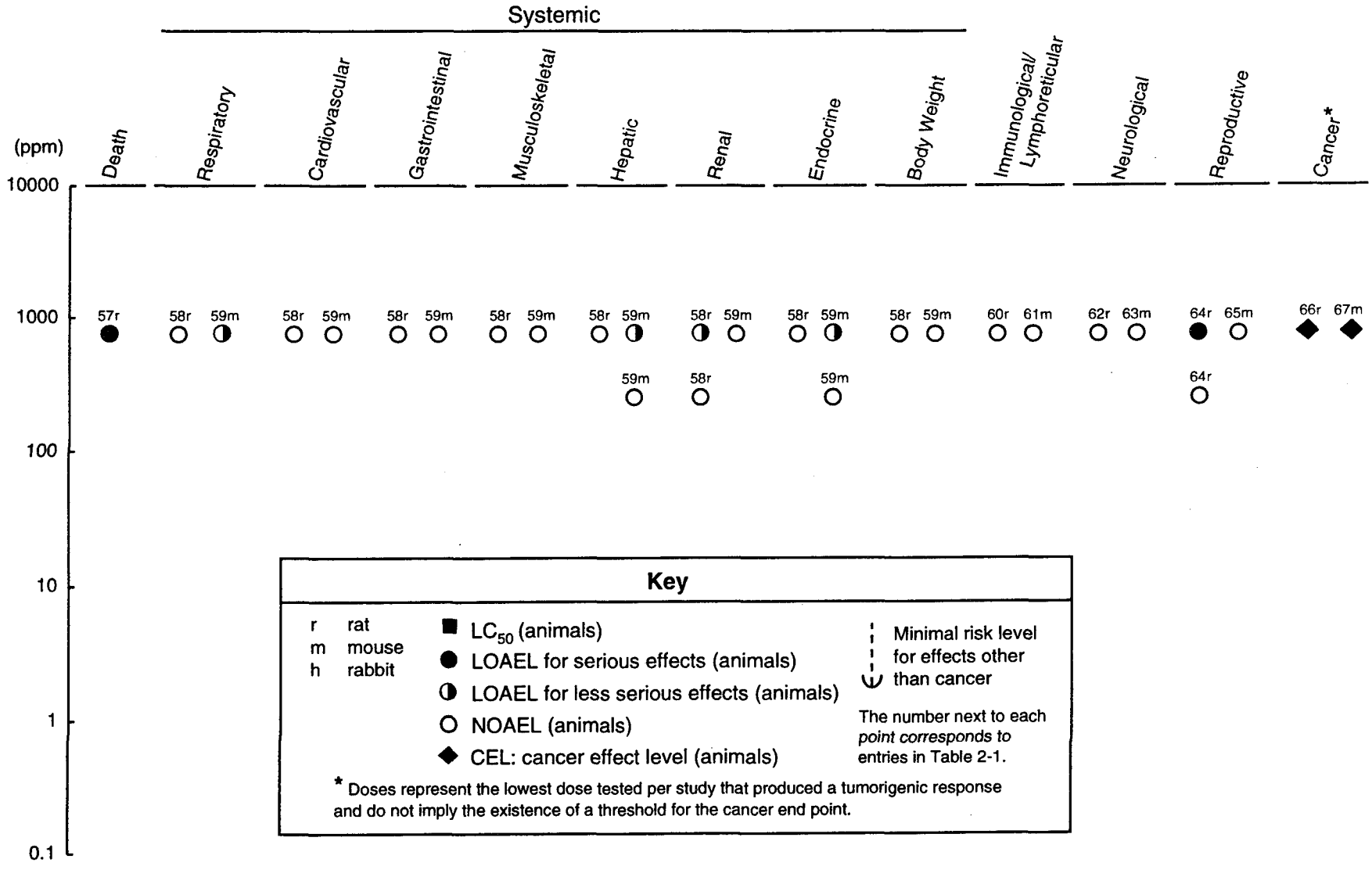


Figure 2-1. Levels of Significant Exposure to Ethylbenzene - Inhalation (cont.)

Chronic (≥365 days)



No studies were located describing cardiovascular, gastrointestinal, musculoskeletal, renal, endocrine, dermal, body weight, or metabolic effects in humans, or dermal effects in animals after inhalation exposure to ethylbenzene.

The systemic effects observed after inhalation exposure are discussed below. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

Respiratory Effects. Throat irritation and chest constriction were reported in the six male volunteers acutely exposed to levels of ethylbenzene in the air as low as 2,000 ppm (Yant et al. 1930). Symptoms became more extreme following exposure to 5,000 ppm. No other significant respiratory changes were reported. The utility of these results is limited because the exposure durations necessary for these effects to occur were not clearly described and the ethylbenzene used for testing reportedly contained small amounts of impurities (e.g., benzol and diethylbenzene). In addition, the methods used to calculate the actual vapor concentration of ethylbenzene were not well described, making it difficult to determine the accuracy of the methods. In case studies involving a male and a female patient, no respiratory effects were observed when the patients were exposed to 55.3 ppm ethylbenzene for 15 minutes in an inhalation chamber (Moscato et al. 1987).

Microscopic examination of tissues from Fischer 344 rats and B6C3F_1 mice exposed to 1,200-2,400 ppm ethylbenzene via inhalation for 4 days showed pulmonary congestion in animals that had died. However, no information on the cause of death was provided; therefore, it is not known if these effects are treatment-related (Biodynamics 1986; Cragg et al. 1989). No effects were seen in Sprague-Dawley rats exposed to 2,000 ppm for 3 days (Toftgard and Nilsen 1982) or New Zealand White rabbits exposed to doses up to 2,400 ppm for 4 days (Biodynamics 1986; Cragg et al. 1989). The concentration of ethylbenzene required to decrease the respiratory rate in mice by 50% (RD_{50}) after inhalation exposure has been determined (De Ceaurriz et al. 1981; Nielsen and Alarie 1982). These values were reported to be 1,432 ppm in male Swiss OFi mice (De Ceaurriz et al. 1981) and 4,060 ppm in Swiss Webster mice exposed to ethylbenzene (Nielsen and Alarie 1982). Respiratory depression was also observed in Swiss Webster mice by Nielsen and Alarie (1982) after intratracheal administration of 4,000 ppm ethylbenzene for 30 minutes. Guinea pigs (strain unspecified) were exposed to ethylbenzene vapor at various concentrations and acute durations (Yant et al. 1930). Nasal irritation was observed in animals exposed to 1,000 ppm for 8 and 3 minutes and in animals exposed to 2,000, 5,000, and 10,000 ppm for 480, 30, and 10 minutes, respectively. Gross

histopathology revealed congestion and edema in the lungs, with an increase in the severity of damage with increased exposure concentration (dose not specified).

Andrew et al. (198 1) investigated the teratologic effects of ethylbenzene exposures in Wistar rats exposed to 0,97, or 959 ppm ethylbenzene for 7 hours a day, 5 days a week for 3 weeks. They were then mated and exposed to ethylbenzene (0,96, or 985 ppm) 7 hours a day, 7 days a week through gestational day (Gd) 19. The rats were then sacrificed and examined at Gd 21. No adverse effects on lung histopathology were found. New Zealand White rabbits dosed at the same levels for 3 weeks prior to mating and after mating until Gd 24 also exhibited no adverse histopathological effects on lung tissue at evaluation on Gd 30. No adverse pulmonary effects were reported when $B6C3F_1$ mice (Cragg et al. 1989) and Fischer 344 rats (Cragg et al. 1989) were exposed to concentrations of ethylbenzene at 782 ppm for 4 weeks. New Zealand White rabbits exposed to concentrations as high as 1,610 ppm for 4 weeks also showed no adverse effects (Cragg et al. 1989).

In a series of studies in which Rhesus monkeys, rats, rabbits, and guinea pigs were exposed for 6-7 months to concentrations of ethylbenzene as high as 2,200 ppm, no toxic effects on lung histopathology were reported in any of the laboratory animals (Wolf et al. 1956). These parameters (i.e., toxic end points), however, were not well defined and may account for differing respiratory depression (RD_{50}) results reported in mice due to sensory irritation at 1,432 and 4,060 ppm by De Ceaurriz et al. (198 1) and Nielsen and Alarie (1982), respectively. The utility of the study by Wolf et al. (1956) is further limited by a general lack of study details (e.g., no exposure or control data were provided).

In the report of a go-day inhalation study, it was noted that both male and female Fischer 344/N rats exposed to 0, 99.4, 246,498,740, or 975 ppm ethylbenzene developed lung lesions and hyperplastic bronchiaVmediastina1 lymph nodes at doses of 246 ppm and above (NTP 1992). These effects were not seen in the exposed $B6C3F_1$ mice in the same study (NTP 1992). In addition, in the rats, increased relative lung weight was observed in males at 975 ppm, whereas female rats exhibited increased absolute and relative lung weight at 246 ppm ethylbenzene. It was the opinion of the NTP Pathology Working Group that “the pulmonary lesions and lymph node hyperplasia were more typical of an infectious agent than a response to the test compound.” In the companion chronic-duration inhalation exposure of male and female Fischer 344 rats and $B6C3F_1$ mice to doses of 0, 75, 250, or 750 ppm for up to 2 years (103-104 weeks), no significant treatment-related histopathological effects were noted on respiratory tissue (NTP 1996).

Cardiovascular Effects. No adverse histopathological effects were reported for cardiac tissue in Fischer 344 rats or B6C3F_1 mice exposed to concentrations of ethylbenzene up to 782 ppm for 5 days a week, 6 hours a day for 4 weeks, or New Zealand White rabbits exposed to concentrations up to 1,610 ppm for 4 weeks (Cragg et al. 1989). In the report of a 90-day inhalation study, it was noted that neither male or female Fischer 344/N rats, nor B6C3F_1 mice exposed to 0, 99.4,246,498, 740, or 975 ppm ethylbenzene 5 days a week, 6 hours a day exhibited any adverse histopathological changes in cardiac tissue (NTP 1992). A similar lack of cardiovascular effects was noted in the companion chronic-duration inhalation exposure of male and female Fischer 344 rats and B6C3F_1 mice to doses of 0,75,250, or 750 ppm for up to 2 years (103-104 weeks) (NTP 1996).

A series of experiments using Rhesus monkeys, rats, rabbits, and guinea pigs exposed for 6-7 months to ethylbenzene concentrations ranging from 400 to 2,200 ppm re;orted no changes in the gross appearance of the heart or abnormal histopathological changes in cardiac tissue (Wolf et al. 1956). This study, however, is of little value because of a lack of study details (e.g., no cardiovascular data were presented), small number of study animals (e.g., one to two rabbits and monkeys), and poor definition of the parameters monitored.

Gastrointestinal Effects. In animals, a series of experiments using Fischer 344 rats and B6C3F_1 mice exposed to ethylbenzene concentrations as high as 782 ppm and New Zealand White rabbits exposed to ethylbenzene concentrations as high as 1,610 ppm for 4 weeks reported no changes in the gross appearance and no abnormal histopathological changes in the intestines (Cragg et al. 1989). In the report of a go-day inhalation study, it was noted that neither male or female Fischer 344/N rats, nor B6C3F_1 mice exposed to 0, 99.4,246,498,740, or 975 ppm ethylbenzene exhibited any adverse histopathological changes in gastrointestinal tissue, including cecum, colon, duodenum, esophagus, ileum, jejunum, and stomach (including forestomach and glandular stomach) (NTP 1992). No adverse histopathological effects were noted in the gastrointestinal tissues of male and female Fischer 344/N rats or B6C3F_1 mice exposed to concentrations up to 750 ppm for up to 2 years (NTP 1996).

Hematological Effects. Two studies involving long-term monitoring of workers occupationally exposed to ethylbenzene showed conflicting results with respect to effects on the hematopoietic system (Angerer and Wulf 1985; Bardodej and Cirek 1988). In one human study involving workers chronically exposed to organic solvents containing ethylbenzene, the average number of lymphocytes increased ($p=0.05$) and hemoglobin levels decreased ($p=0.011$) in exposed individuals (n=35 males) compared with controls (Angerer and Wulf 1985). The average level of ethylbenzene in the blood of these workers at

which correlations were seen between exposure and hematological effects was 61.4 µg/L. Blood cell values of male workers examined in 1983 and 1984 showed average lymphocyte levels increased 68.8% and 41.5%, respectively, compared to controls. Average hemoglobin values decreased 7.1% and 5.2% in male workers examined in 1983 and 1984, respectively. Results showed that the hematopoetic system might be the target organ of a chronic exposure to alkylbenzene. However, whether the effect is due to one of the alkylbenzenes (e.g., ethylbenzene) or to the mixture was undetermined. Concomitant exposure to lead in these workers could be a confounding factor. The use of the median lead level, rather than the mean and variance of this measurement, could result in a lower estimate of the impact of concomitant exposure to lead. No adverse hematological effects were seen in a long-term study (20 years) on 200 male workers occupationally exposed to unspecified concentrations of ethylbenzene (Bardodej and Cirek 1988). Given the overall lack of a substantial amount of quantitative exposure data and simultaneous exposure to other hazardous chemicals such as xylene isomers, *n*-butanol, and C-9 aromatic hydrocarbons in the study of Angerer and Wulf (1985), these results are inadequate for evaluating hematological effects of ethylbenzene following inhalation exposure in humans.

Experiments with rats demonstrated a statistically significant increase in platelet counts in male Fischer 344 rats and a statistically significant increase in the mean total leukocyte count in female Fischer 344 rats exposed to 782 ppm ethylbenzene for 4 weeks (Cragg et al. 1989). Hematological parameters did not change for B6C3F_1 mice or New Zealand White rabbits exposed to the same or higher concentrations.

The effects of ethylbenzene on bone marrow counts and total blood counts were investigated in a series of experiments using Rhesus monkeys, rats, mice, rabbits, and guinea pigs exposed for 6-7 months to concentrations ranging from 400 to 2,200 ppm (Wolf et al. 1956). No effects were reported in any of the animals tested, but a number of limitations (e.g., small number of test animals) and poorly defined parameters (e.g., specific toxic end points that were investigated) may explain these results, which are different that those of Cragg et al. (1989). However, In a report of a 90-day inhalation study in Fischer 344/N rats and B6C3Fi mice, no adverse hematological effects were noted following exposure to ethylbenzene vapor concentrations of up to 975 ppm (NTP 1992). Based on the available data, no definitive conclusion can be drawn regarding the effect of ethylbenzene on hematological parameters.

Musculoskeletal Effects. Histopathological examination of bone tissue from Fischer 344 rats, B6C3F, mice, and New Zealand White rabbits exposed to concentrations of ethylbenzene up to 782 ppm in rats and mice, and 1,610 ppm in rabbits for 4 weeks revealed no bone tissue abnormalities in any of the

animals examined (Cragg et al. 1989). Neither was any adverse effect on bone tissue seen in Fischer 344/N rats or B6C3F$_1$ mice exposed to 975 ppm ethylbenzene for 90 days, or 750 ppm for up to 2 years (NTP 1992, 1996). Given the limited data on musculoskeletal effects following ethylbenzene inhalation exposure, no conclusions can be drawn.

Hepatic Effects. In a 20-year study of 200 male workers occupationally exposed to an undetermined concentration of ethylbenzene, no cases of liver lesions or significant differences in liver function tests between exposed and nonexposed workers were reported (Bardodej and Cirek 1988). During the entire investigation period the risk of ethylbenzene exposure in this production plant was reported as negligible.

The results from several studies have suggested that hepatic effects may result from inhalation exposure to ethylbenzene in laboratory animals. Studies with rats, mice, and rabbits showed differences in effects across species (Andrew et al. 1981; Biodynamics 1986; Cragg et al. 1989; Elovaara et al. 1985, 1982; Toftgard and Nilsen 1982; Wolf et al. 1956). No definitive conclusions can be drawn because limitations are present in many of the studies. Effects include biochemical changes, histopathological alterations, and an increase of liver weight relative to body weight. These changes may be an adaptive response, but potential toxicity cannot be ruled out.

Hepatic congestion was observed upon microscopic examinations of liver tissue from Fischer 344 rats exposed to 2,400 ppm for 4 days and from B6C3F$_1$ mice exposed to 1,200 ppm or 2,400 ppm for 4 days (Biodynamics 1986; Cragg et al. 1989). Both groups of animals had died prior to termination of the experiment. This liver congestion, however, may have been a secondary effect and may not be treatmentrelated. No cause of death was reported for any of the animals. Biochemical changes (e.g., increases in cytochrome P-450 concentration, NADPH-cytochrome reductase, 7-ethoxycoumarin 0-deethylase [Toftgard and Nilsen 19821, and UDP glucuronyl-transferase) were reported in rats exposed to 2,000 ppm ethylbenzene concentrations for 3 days and concentrations as low as 300 ppm for up to 16 weeks (Elovaara et al. 1985). Electron microscopy also showed changes in hepatocyte ultrastructure (e.g., smooth endoplasmic reticulum proliferation, slight degranulation of rough endoplasmic reticulum) in rats beginning 2 weeks after exposure to ethylbenzene (Elovaara et al. 1985). Fouchecourt and Riviere (1996) also reported induction of hepatic enzymes (7-ethoxyresorufm 0-deethylase) in male and female Sprague-Dawley rats and wild Norway rats exposed for up to 2 weeks in the laboratory to soil from a contaminated petrochemical waste site that contained 0.2 ppm ethylbenzene among many other constituents. A slight increase in hepatic catalase activity was also seen after 30-60 days of exposure to the contaminated soil. In general, enzyme induction enhances the metabolism of ethylbenzene and may be considered an adaptive

phenomenon rather than a hepatotoxic effect. Increased liver-to-body-weight ratios were observed in male Sprague-Dawley rats exposed to 2,000 ppm ethylbenzene for 3 days (Toftgard and Nilsen 1982), Fischer 344 rats exposed to 400 ppm ethylbenzene for 4 days (Biodynamics 1986; Cragg et al. 1989), and Fischer 344 rats and B6C3F_1 mice exposed to 782 ppm ethylbenzene for 4 weeks (Cragg et al. 1989). Andrew et al. (1981) also reported increased relative liver weight in pregnant and nonpregnant Wistar rats and pregnant New Zealand White rabbits exposed to 959 and 962 ppm ethylbenzene, respectively, for 3 weeks prior to mating and throughout gestation. As with intracellular and biochemical changes, the significance of the increased relative liver weight with regard to possible health effects is unclear. No hepatic effects were observed in New Zealand White rabbits exposed to 2,400 ppm for 4 days, or 1,610 ppm for 4 weeks (Biodynamics 1986; Cragg et al. 1989).

Ethylbenzene exposure by inhalation for 6-7 months caused increased liver weights in Rhesus monkeys (600 ppm), rats (400 ppm), and guinea pigs (600 ppm), and histopathological changes including cloudy swelling in the liver of rats (2,200 ppm) (Wolf et al. 1956). No hepatic effects were reported in rabbits at 1,250 ppm (Wolf et al. 1956). The utility of this study, however, is limited by the lack of study details and statistical analysis of the histopathology results. Increased relative liver weights were also noted in a report of a 90-day inhalation study in which Fischer 344/N rats and B6C3F_1 mice were exposed to 249 ppm and 740 ppm ethylbenzene, respectively (NTP 1992). However, no corresponding organ dysfunction or histopathological change accompanied this observation. When Fischer 344/N rats and B6C3F_1 mice were exposed to concentrations of ethylbenzene up to 750 ppm for up to 2 years, male mice, but not rats, exhibited an increased incidence of syncytial alterations of the hepatocytes, hypertrophy, and hepatic necrosis; female mice exhibited an increased incidence of eosinophilic foci (NTP 1996).

Renal Effects. Renal effects, manifested as histopathological changes, enzymatic changes, or increased kidney-to-body-weight ratios, have been observed in a number of species following inhalation exposure to ethylbenzene (Andrew et al. 1981; Biodynamics 1986; Cragg et al. 1989; Elovaara et al. 1985; NTP 1992; Toftgard and Nilsen 1982; Wolf et al. 1956). The significance of these changes with regard to possible health effects is not known, but these studies suggest variations across species, indicating that rats and mice may be more susceptible to ethylbenzene-induced renal effects than rabbits, guinea pigs, and monkeys. However, this is difficult to determine given weaknesses (e.g., poor study details, lack of statistical analysis, small number of animals used) in many of these studies. Enzymatic changes in the kidney (e.g., increased concentration of 7-ethoxycoumarin, 0-deethylase, UDP glucuronyl-transferase, NADPHcytochrome c reductase) were reported in Sprague-Dawley rats following a 3-day exposure to 2,000 ppm

ethylbenzene (Toftgard and Nilsen 1982). Increased kidney-to-body-weight ratios were reported following a 4-day exposure of Fischer 344 rats to 1,200 ppm; and renal congestion was reported in Fischer 344 rats and B6C3F$_1$ mice following a 4-day exposure to 1,200 ppm ethylbenzene, but not in New Zealand White rabbits exposed to 2,400 ppm ethylbenzene for the same period of time (Biodynamics 1986; Cragg et al. 1989). These effects were not unusual in animals that died and were not exsanguinated. Therefore, this effect may be a secondary effect and may not be treatment-related.

Longer exposure durations produced renal effects at lower ethylbenzene exposure concentrations. Andrew et al. (1981) reported increased relative kidney weight in pregnant Wistar rats exposed to 959 ppm, followed by exposure to 985 ppm ethylbenzene, but no changes in pregnant New Zealand White rabbits exposed to 962 ppm ethylbenzene for 3 weeks prior to mating and throughout gestation. Dose-related increases in 7-ethoxycoumarin 0-deethylase, UDP glucuronyl-transferase and glutathione were reported in Wistar rats following a 5-16-week exposure to ethylbenzene at concentrations ranging from 50 to 600 ppm (Elovaara et al. 1985). In the same study, significant increases in the kidney-to-body-weight ratio were observed at weeks 2 and 9 in animals exposed to 400 ppm when compared with control animals. No renal changes were reported in Fischer 344 rats or B6C3F$_1$ mice exposed to ethylbenzene concentrations as high as 782 ppm for 4 weeks or in New Zealand White rabbits exposed to ethylbenzene concentrations as high as 1,610 ppm for the same duration (Cragg et al. 1989).

In rats, a slight increase in kidney weight was observed at 400 ppm, and swelling of the tubular epithelium in the kidney was observed in rats exposed to 600 ppm ethylbenzene for up to 7 months (Wolf et al. 1956). No toxic effects were reported in rabbits, guinea pigs or Rhesus monkeys. The usefulness of this study, however, is limited by the lack of study details and statistical analysis of the histopathology data. In a report of a 90-day inhalation study, it was noted that Fischer 344/N rats and B6C3F$_1$ mice exhibited increased relative kidney weights at ethylbenzene concentrations of 740 ppm and 975 ppm, respectively (NTP 1992). Regeneration of renal tubules in the kidneys of male rats was also seen in all exposure groups, including controls. It was noted that the degree of regeneration was somewhat greater in the 975 ppm group compared to the controls; however, this difference was not statistically significant. In the companion 2-year bioassay (NTP 1996), rats exhibited increased incidence of renal tubule hyperplasia at 750 ppm, but mice were not adversely affected.

Endocrine Effects. Three studies in animals addressed histopathological effects in endocrine organs after intermediate-duration inhalation exposure to ethylbenzene. Microscopic examination of the adrenals,

pancreas, pituitary, and thyroid/parathyroid glands from Fischer 344 rats, $B6C3F_1$ mice, and New Zealand White rabbits exposed to 782 ppm (rats and mice) or 1,610 ppm (rabbits) ethylbenzene for 6 hours a day, 5 days a week for 4 weeks showed no changes (Cragg et al. 1989). The NTP (1992) go-day study indicated no histopathological effect on the adrenal glands, pancreas, parathyroid glands, pituitary gland, or thyroid gland from Fischer 344/N rats and $B6C3F_1$ mice exposed to 975 ppm ethylbenzene. Wolf et al. (1956) evaluated the effects of inhalation exposure of Rhesus monkeys, rats, guinea pigs, and rabbits to ethylbenzene for 5 days a week, 7-8 hours a day for 6-7 months on adrenal and pancreatic tissue. No effect was seen in Rhesus monkeys at concentrations up to 600 ppm, in rats at 2,200 ppm, or in guinea pigs and rabbits at 1,250 ppm.

No adverse effect on endocrine glands was observed in rats exposed to concentrations of 75-750 ppm in the companion 2-year bioassay (NTP 1996). However, mice exposed to the same concentrations of ethylbenzene for 2 years exhibited an increased incidence of follicular cell hyperplasia in the thyroid gland at the high dose. In female mice exposed to 250 and 750 ppm ethylbenzene, the incidences of hyperplasia of the pituitary gland pars distalis were significantly greater than those in the control group.

Ocular Effects. Ethylbenzene concentrations of 1,000 ppm have been shown to cause momentary ocular irritation, a burning sensation, and profuse lacrimation in humans (Thienes and Haley 1972; Yant et al. 1930). These effects became more severe in humans exposed to 2,000 ppm ethylbenzene and intolerable at concentrations of 5,000 ppm or higher (Yant et al. 1930). The strength of these results, however, is diminished by a number of limitations (e.g., unclear exposure durations, impurities in ethylbenzene, and limited information on methodology for analysis of the concentrations used). Cometto-Muniz and Cain (1995) measured eye irritation in humans after exposure to ethylbenzene vapor. Eye irritation was observed at 10,000 ppm.

Similar ocular effects to those in humans were seen in animals exposed to ethylbenzene vapors. Eye irritation accompanied by tearing was observed in guinea pigs 8 minutes following exposure to 1,000 ppm ethylbenzene and 1 minute following exposure to 2,000-10,000 ppm ethylbenzene (Yant et al. 1930). Tegeris and Balster (1994) reported lacrimation and palpebral closure in male CFW mice after 20 minutes of exposure to 2,000 ppm ethylbenzene. After 4 days of inhalation exposure to 1,200 ppm ethylbenzene, Fischer 344 rats exhibited lacrimation (Biodynamics 1986; Cragg et al. 1989). $B6C3F_1$ mice and New Zealand White rabbits exhibited lacrimation after exposure to 400 ppm. After 4 weeks of exposure to 382 ppm, rats showed sporadic lacrimation, whereas mice and rabbits showed no ocular effects at 782 ppm

and 1,610 ppm, respectively (Cragg et al. 1989). No ocular effects were seen in Fischer 344/N rats and $B6C3F_1$ mice after a 13-week exposure to 975 ppm ethylbenzene (NTP 1992).

Ocular effects observed in humans and animals after inhalation exposure to ethylbenzene are presumed to be due to direct contact of the eyes with ethylbenzene vapor. These effects are discussed in Section 2.3.3.2.

Body Weight Effects. Studies in animals have addressed body weight effects of acute- and intermediate-duration inhalation exposure to ethylbenzene. After 4 days of exposure, Fischer 344 rats, $B6C3F_1$ mice, and New Zealand White rabbits showed no adverse effect on body weight at 1,200,400, and 2,400 ppm, respectively (Biodynamics 1986; Cragg et al. 1989). Similarly, Romanelli et al. (1986) saw no effect on body weight in New Zealand White rabbits after 7 days of exposure to 750 ppm.

Andrew et al. (1981) reported no change in body weight in pregnant Wistar rats or New Zealand White rabbits exposed to 985 and 962 ppm ethylbenzene, respectively, for 3 weeks prior to mating and throughout gestation. Elovaara et al. (1985) reported a decrease in body weight gain of 26-48% at weeks 2, 5, and 9, but not at week 16 in male Wistar rats exposed to 600 ppm ethylbenzene 6 hours a day, 5 days a week. No adverse effect on body weight was observed in Fischer 344 rats, $B6C3F_1$ mice, and New Zealand White rabbits exposed to 782 ppm (rats and mice) or 1,610 ppm (rabbits) ethylbenzene for 6 hours a day, 5 days a week for 4 weeks (Cragg et al. 1989). Wolf et al. (1956) evaluated the effects of inhalation exposure of Rhesus monkeys, rats, guinea pigs, and rabbits to ethylbenzene for 7-8 hours a day, 5 days a week for 6-7 months on body weight. No effect was seen in monkeys at concentrations up to 600 ppm, or in rats or rabbits at 1,250 ppm. Rats exposed to 2,200 ppm and guinea pigs exposed to 1,250 ppm showed some growth depression (data not shown). The NTP (1992) 90-day study indicated no effect on body weight in Fischer 344/N rats and $B6C3F_1$ mice exposed to 975 ppm ethylbenzene. Similarly, no significant effect on body weight was observed in the companion 2-year study in which rats and mice were exposed to concentrations of ethylbenzene of up to 750 ppm (NTP 1996).

Metabolic Effects. Biochemical changes in the liver and kidney (e.g., increases in microsomal protein content, NADPH-cytochrome reductase, 7-ethoxycoumarin 0-deethylase, and UDP glucuronyl-transferase) were reported in rats exposed to ethylbenzene concentrations as low as 300 ppm after 5 weeks of exposure, and at 600 ppm after 16 weeks (Elovaara et al. 1985). Electron microscopy also showed changes in hepatocyte ultrastructure (e.g., smooth endoplasmic reticulum proliferation, slight degranulation of rough endoplasmic reticulum) in rats beginning 2 weeks after exposure to ethylbenzene, indicating metabolic

activation of the liver. Increased enzyme activities in liver and kidney (cytochrome P-450 concentration, increased NADPH-cytochrome C reductase activity, 7-ethoxyresorufin, hydroxylation of *n*-hexane, and metabolism of benz[a]pyrene) were also observed in Sprague-Dawley rats exposed to 2,000 ppm ethylbenzene for 3 days (Toftgard and Nilsen 1982)

Other Systemic Effects. Fischer 344 rats exposed to 1,200 ppm ethylbenzene for 4 days exhibited yellow or brown anogenital staining (Biodynamics 1986; Cragg et al. 1989). Andrew et al. (1981) reported no change in food consumption in pregnant Wistar rats or New Zealand White rabbits exposed to 985 and 962 ppm ethylbenzene, respectively, for 3 weeks prior to mating and throughout gestation.

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were found regarding immunological effects in humans following inhalation exposure to ethylbenzene.

Andrew et al. (1981) reported increased relative spleen weight in pregnant Wistar rats, but not in pregnant New Zealand White rabbits exposed to 959 and 962 ppm ethylbenzene, respectively, for 3 weeks prior to mating and throughout gestation. Cragg et al. (1989) examined bone marrow (sternum), lymph nodes, thymic region, and spleen from Fischer 344 rats, $B6C3F_1$ mice, and New Zealand White rabbits exposed to 782 ppm (rats and mice) or 1,610 ppm (rabbits) for 4 weeks. No changes were seen in the tissues. Wolf et al. (1956) evaluated the effects on body weight of inhalation exposure of guinea pigs, and rabbits to ethylbenzene for 5 days a week, 7-8 hours a day for 6-7 months. No effect was seen the gross appearance of the spleen, or the bone marrow in guinea pigs or rabbits at 1,250 ppm. Both the NTP (1992) 90-day study and the NTP 2-year bioassay (NTP 1996) indicated no treatment-related effect on the histopathology of several tissues, including bronchial lymph nodes, regional lymph nodes, mandibular and mesenteric lymph nodes, mediastinal lymph nodes, spleen, or thymus in Fischer 344/N rats and $B6C3F_1$ mice exposed to 975 ppm ethylbenzene for 90 days or 750 ppm for 2 years.

The highest NOAELs for immunological and lymphoreticular effects in each species for intermediate- or chronic-duration exposure are reported in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.4 Neurological Effects

Symptoms of dizziness accompanied by vertigo have been observed in humans acutely exposed to air concentrations of ethylbenzene ranging from 2,000 to 5,000 ppm (Yant et al. 1930). Complete recovery occurs if exposure is not prolonged. This study had a number of weaknesses (e.g., unclear exposure durations, impurities in ethylbenzene, and limited information on the methodology for analysis of vapor concentrations). No studies were found regarding neurological effects in humans following intermediate- or chronic-duration exposure.

The primary effects in animals following acute exposure to high air concentrations of ethylbenzene are neurological effects. Central nervous system depression and ataxia were observed in guinea pigs exposed to 2,000 ppm ethylbenzene for acute-duration periods (Yant et al. 1930). Moderate activation in motor behavior was observed in CFY rats following a 4-hour inhalation exposure to levels of ethylbenzene ranging from 400 to 1,500 ppm (Molnar et al. 1986). In the same study, narcotic effects were observed in CFY rats at ethylbenzene concentrations from 2,180 to 5,000 ppm. This study is limited by a lack of methodological detail and appropriate statistical analysis. In addition, Nielsen and Alarie (1982) were unable to determine whether respiratory effects observed in Swiss-Webster mice exposed via intratracheal instillation to various concentrations of ethylbenzene up to 7,800 ppm or 9,640 ppm by inhalation for a duration of 30 minutes were due to sensory irritation of the upper respiratory tract or central nervous system effects. Tegeris and Balster (1994) evaluated the neurobehavioral effects of ethylbenzene in adult male CFW (Charles River Swiss) albino mice exposed to 0, 2,000,4,000, or 8,000 ppm for 20 minutes. Ethylbenzene at 2,000,4,000, and 8,000 ppm produced changes in posture; decreased arousal and rearing; increased ease of handling; disturbances of gait, mobility, and righting reflex; decreased forelimb grip strength; increased landing foot splay; and impaired psychomotor coordination. These acute effects were short-lived and more pronounced during exposure than after exposure, with recovery beginning within minutes of removal from the exposure chamber. Sensorimotor reactivity also decreased. Salivation, prostration, and/or reduced activity were observed in Fischer 344 rats and $B6C3F_1$ mice exposed to 2,400 or 1,200 ppm ethylbenzene, respectively, for 4 days (Biodynamics 1986; Cragg et al. 1989). However, New Zealand White rabbits exposed to 2,400 ppm ethylbenzene for the same period of time showed no adverse behavioral effects. In addition, no significant dose-related behavioral changes and no histopathological alterations were reported in rats or mice exposed to concentrations of up to 782 ppm for 6 hours a day, 5 days a week for 4 weeks, although sporadic salivation was noted in rats at doses of 382 ppm and above (Cragg et al. 1989). Similarly, no behavioral changes or histopathological alterations

were observed in rabbits exposed to concentrations up to 1,610 ppm ethylbenzene for 4 weeks (Cragg et al. 1989). Changes in dopamine and other biochemical alterations were observed in Sprague-Dawley rats (Andersson et al. 1981) and New Zealand White rabbits (Mutti et al. 1988; Romanelli et al. 1986) exposed for 3-7 days to ethylbenzene concentrations of 2,000 and 750 ppm, respectively. Frantik et al. (1994) studied acute neurotoxicity of ethylbenzene in Wistar rats and H strain mice. Exposure to 245 and 342 ppm, respectively, resulted in a 30% depression of evoked electrical activity in the brain immediately after exposure. In a 90-day study (NTP 1992), Fischer 344/N rats and $B6C3F_1$ mice showed no adverse histopathological effects on brain tissue at doses up to 975 ppm. Similarly, no adverse effects were noted in the brain tissues of rats and mice exposed to concentrations of ethylbenzene of up to 750 ppm in the companion 2-year bioassay (NTP 1996). Differences in results in the studies using rats (Andersson et al. 1981; Molnar et al. 1986) and rabbits (Mutti et al. 1988; Romanelli et al. 1986) exposed to ethylbenzene are probably due to parameters monitored, duration of exposure, and analytical technique. Differences in results can also be attributed to differences in species studied (Biodynamics 1986; Cragg et al. 1989).

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to ethylbenzene.

No reproduction studies over one or more generation of animals were located for inhalation exposure to ethylbenzene. After acute exposure to concentrations as high as 2,400 ppm ethylbenzene for 4 days, no histopathological changes were noted in the testes of Fischer 344 rats, $B6C3F_1$ mice, or New Zealand White rabbits (Biodynamics 1986; Cragg et al. 1989). Ungvary and Tatrai (1985) evaluated the embryotoxic effects of benzene and its alkyl derivatives in CFY rats, CFLP mice, and New Zealand White rabbits. Pregnant rats, mice, and rabbits were exposed by inhalation to concentrations up to 553, 115, and 230 ppm respectively, continuously during organogenesis. Rats exhibited increased postimplantation death in all treated groups 2138 ppm, whereas mice exhibited no adverse effects. Rabbits exhibited increased abortions at the high dose.

No testicular histopathological abnormalities were reported in Fischer 344 rats and $B6C3F_1$ mice exposed to concentrations as high as 782 ppm and New Zealand white rabbits exposed to ethylbenzene concentrations as high as 1,610 ppm for 4 weeks (Cragg et al. 1989). Pre-gestational exposure for 3 weeks and gestational exposure of female Wistar rats and New Zealand White rabbits to concentrations of approximately 100 or 1,000 ppm ethylbenzene resulted in no conclusive evidence of reproductive effects in either species (Andrew et al. 1981).

NTP (1992) reported no effect on sperm or testicular morphology, or the length of the estrous cycle in Fischer 344/N rats or $B6C3F_1$ mice exposed to 975 ppm ethylbenzene for 90 days. For rats in the highdose group, the decrease in epididymal weight was not considered biologically significant since spermatid counts, sperm motility, and caudal weight were normal. Inhalation exposure of male Rhesus monkeys and rabbits to 600 ppm ethylbenzene for 6 months produced degeneration of germinal epithelium in the testes of one monkey and one rabbit (Wolf et al. 1956). Because there was only one male per exposure group, and because insufficient details on the study protocol were provided, the usefulness of this study is limited. No adverse histopathological effects were seen in the testes of rats or guinea pigs exposed to concentrations up to 1,250 or 600 ppm, respectively, for 6-7 months. Based on this limited evidence, no conclusions can be drawn concerning the possible reproductive consequence of this effect in animals.

In the NTP-sponsored 2-year bioassay, the incidence of interstitial cell adenoma in male Fischer 344/N rats exposed to 750 ppm was significantly greater than in the control group and slightly exceeded the historical control range for inhalation studies (NTP 1996). The incidence of bilateral testicular adenoma was also significantly increased in males exposed to 750 ppm. Adenoma in the testes was observed in 36 of 50, 33 of 50,40 of 50, and 44 of 50 male rats exposed to 0, 75, 250, and 750 ppm, respectively. No adverse effects on the reproductive tissues of male and female $B6C3F_1$ mice were observed (NTP 1996).

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species for acute-, intermediate-, and chronic-duration are recorded in Table 2- 1 and plotted in Figure 2- 1.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans following inhalation exposure to ethylbenzene.

The developmental effects of inhalation exposure to ethylbenzene have been studied in rats, mice, and rabbits (Andrew et al. 1981; Ungvary and Tatrai 1985). In rats, exposure during gestation to ethylbenzene for 24 hours a day for 9 days at doses ranging from 138 to 552 ppm resulted in fetal resorption and retardation of skeletal development in surviving fetuses (Ungvary and Tatrai 1985). Increased incidence of extra ribs and anomalies of the urinary tract were observed at the 552 ppm dose level. No effects were observed after exposure to 138 ppm for 6 hours a day for 9 days (Ungvary and Tatrai 1985). Maternal toxicity was reported to be moderate and dose-dependent, but no data were presented. Andrew et al. (1981) investigated the teratologic effects of ethylbenzene exposures to rats. Wistar rats were exposed to 0,100, or 1,000 ppm (average exposure chamber concentration measured at 0,97, or 959 ppm, respectively) ethylbenzene for 7 hours/day, 5 days/week for 3 weeks. They were then mated and exposed to 0, 100, or 1,000 ppm (average exposure chamber concentration measured at 96 or 985 ppm, respectively) ethylbenzene 7 hours/day, 7 days/week through Gd 19. The rats were then killed and examined at Gd 21. Litters were examined for the presence of external, visceral, and skeletal abnormalities, as well as incidence of growth retardation and intrauterine mortality. There was no maternal toxicity, as shown by no histopathological changes in the ovaries, lung, kidney, or liver, and there were no treatment-related effects on food consumption or body weight in the rats. However, relative liver and kidney weights were significantly increased in both groups exposed to 1,000 ppm during gestation compared to the pregnant control groups. Relative liver weights of non-pregnant rats were also elevated for the same high-level exposure groups. There were no significant increases in major malformations or minor anomalies in any of the exposed groups. Increased incidence of fetuses with extra ribs ($p<0.05$) was noted in A-L (0-100 ppm), A-H (0-1,000 ppm) and H-H (1,000-1,000 ppm) exposure groups while rudimentary rib incidence was elevated only in the A-H (0-1,000 ppm) group. When gestational exposure is considered for comparative purposes, only the high dosed groups had increased incidence of supernumerary ribs on the basis of percent of litters affected (69% for A-H [0-1,000 ppm] versus 5 1.6% for H-H [1,000-1,000 ppm]). The range for all of the air control and low dosed rats was 36.4-48.5%.

Mice exposed to 115 ppm ethylbenzene during gestation demonstrated an increased incidence of anomalies of the urinary tract (Ungvary and Tatrai 1985). The nature of the renal malformation was not characterized and no maternal toxicity was reported.

Reduction in the weight of female fetuses was reported in rabbits exposed to 115 ppm during gestation (Ungvary and Tatrai 1985) but not following longer exposure to higher doses (up to 1,000 ppm) (Andrew et al. 198 1). New Zealand rabbits were artificially inseminated and exposed to 0, 100, or 1,000 ppm

(average exposure chamber concentration measured at 99±9 or 962±76 ppm, respectively) ethylbenzene on Gd 1-24 for 7 hours/day and killed on Gd 30. There were no changes in food consumption or body weights of animals exposed for 24 days to 99 or 962 ppm ethylbenzene. Relative lung and kidney weights were unremarkable. At 962 ppm, absolute and relative liver weights of pregnant rabbits were higher than pregnant control groups. Mean relative weights of kidneys of all pregnant and nonpregnant does were unremarkable. Histological examination of the lungs of the rabbits showed no treatment-related changes. No apparent treatment-related cellular changes occurred in the kidneys. The livers had variable degrees of hepatocellular vocalization characterized by rough, nondiscrete vacuole edges, resembling glycogen deposits; the incidence of this change was evenly distributed among the control and exposed groups. No treatment-related effects were observed in fetal size, placental weight, or intrauterine growth retardation. There were no significant incidences of major malformations, minor anomalies, or common variants in fetal rabbits exposed in utero to ethylbenzene. Maternal toxicity, embryotoxicity, growth retardation, and teratogenicity were not observed in rabbits exposed to 100 or 1,000 ppm ethylbenzene in this study.

As stated above, a statistically significant increase in the incidence of fetuses with supernumerary ribs was observed in rats exposed to 959 ppm ethylbenzene during Gd 1-19 (Andrew et al. 1981). A statistically significant increase in this anomaly was also seen in rats exposed to 959 ppm for 7 hours daily, 5 days a week for 3 weeks just prior to mating followed by exposure during Gd 1-19. However, supernumerary ribs are a non-specific variation often observed in rodent fetuses. No supernumerary ribs were observed in the 97 ppm dose group. Based on this value of 97 ppm, an intermediate-duration inhalation MRL of 1.0 ppm was calculated, as described in the footnote to Table 2-l and in Appendix A.

The published version of the study by Ungvary and Tatrai (1985) has many deficiencies, including poor reporting of the experimental conditions used, absence of significant data concerning the test chemical and generation of the exposure environment, insufficient number of dose levels tested, and details of maternal and fetal observations, including abnormalities. In contrast, the study by Andrew et al. (1981), is well documented, and was conducted according to the testing standards of the U.S. Government that were in force at the time of the study. Even so, the effects seen, and on which the intermediate-duration inhalation MRL was based, were minimal, and may not be relevant to human health. Therefore, the potential for developmental effects following ethylbenzene exposure in humans cannot be ascertained.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-l.

2.2.1.7 Genotoxic Effects

Only one study was found that discussed genotoxic effects in humans after inhalation exposure to a mixture of chemicals, including ethylbenzene. Holz et al. (1995) determined low-level exposure to ethylbenzene and its effect on peripheral lymphocytes in workers in a styrene production plant. Twenty-five exposed workers were compared with 25 non-exposed control employees working at the same company. The concentration of ethylbenzene for exposed workers determined from active air sampling at four different locations (oven house, production control, storage facility, and distillation area) ranged from 365 to 2,340 mg/m^3 (84-539 ppm). Measurements performed at the pump house showed ethylbenzene concentration levels >4,000 mg/m^3 (921 ppm) which exceeded the detection limit of the sampling device. Ethylbenzene concentration levels for control workers ranged from 145 to 290 mg/m^3 (33-67 ppm). Genotoxic monitoring was performed by nuclease P1-enhanced ^{32}P-postlabeling of DNA adducts in peripheral blood monocytes, and DNA single strand breaks, sister chromatid exchange, and micronuclei in lymphocytes. The content of kinetochores in the micronuclei was determined by immunofluorescence with specific antibodies from the serum of calcinosis-Raynaud's phenomenon-oesophageal dismobility-sclerodactyly-telangiectasia syndrome of scleroderma (CREST) patients. Metabolite concentrations in urine of exposed workers confirmed absorption of the ethylbenzene. No genotoxic effects related to exposure were detected by DNA adduct formation or DNA single strand breaks and sister chromatid exchange. Increased kinetochore positive micronuclei in peripheral lymphocytes were observed in the total exposed group ($p=0.007$), exposed smokers ($p=0.045$), and exposed non-smokers ($p=0.035$); the frequency of total micronuclei in peripheral lymphocytes was unchanged. Results from this study are inconclusive with regard to the genotoxic effects of ethylbenzene, since the workers were exposed to a mixture of styrene, ethylbenzene, benzene, toluene, and xylenes. In addition, the sample size of 25 exposed workers and 25 non-exposed controls was very small.

Evaluation of micronucleated erythrocytes from peripheral blood samples from male and female B6C3Fi mice exposed to concentrations of ethylbenzene of up to 750 ppm for 13 weeks showed no increase in the frequency of occurrence (NTP 1996). Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No association has been found between the occurrence of cancer in humans and occupational exposure to ethylbenzene. Only one study was located that monitored the condition of 200 male workers chronically

exposed to ethylbenzene (Bardodej and Cirek 1988). No cases of malignancy in workers monitored for 20 years were reported. However, no conclusions can be drawn from this study because no quantitative exposure information was provided, and the length of time for which the workers were monitored for tumors was only 20 years, which is insufficient for detecting long-latency tumors in humans. No other studies were found regarding cancer effects in humans exposed to ethylbenzene by inhalation.

Information concerning the carcinogenicity of ethylbenzene in animals comes from a recently completed NTP-sponsored bioassay (NTP 1996). Male and female Fischer 344/N rats and B6C3F[1] mice were exposed to 0,75, 250, or 750 ppm ethylbenzene for up to 2 years. Pathological findings in male Fischer 344/N rats exposed to 750 ppm ethylbenzene showed incidences of renal tubule adenoma and adenoma or carcinoma (combined) significantly greater than incidences in the control group. An extended evaluation of the kidneys showed significant increases in incidences of renal tubule adenoma and renal tubule hyperplasia in both male and female rats exposed to 750 ppm ethylbenzene. In males exposed to 750 ppm, the incidence of renal tubule adenoma or carcinoma (combined) was significantly increased. The severity of nephropathy was increased in both male and female rats exposed to 750 ppm ethylbenzene. The incidence of interstitial cell adenoma in males exposed to 750 ppm was significantly greater than in control group and slightly exceeded the historical control range for inhalation studies. The incidence of bilateral testicular adenoma was also significantly increased in males exposed to 750 ppm. Adenoma in the testes was observed in 36 of 50, 33 of 50,40 of 50, and 44 of 50 male rats exposed to 0,75,250, and 750 ppm, respectively. In mice, the incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) were significantly greater in males exposed to 750 ppm than in the controls but were within the NTP historical control range. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly greater in female mice exposed to 750 ppm than in the control group but were within the historical control ranges. The draft report indicates that these results indicate clear evidence of carcinogenicity in male rats, and some evidence of carcinogenicity in female rats and male and female mice.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans following oral exposure to ethylbenzene. However, lethality has been observed in laboratory animals following ingestion of ethylbenzene. The oral LDSO

(lethal dose, 50% kill) for gavage administration of ethylbenzene to Carworth Wistar rats was reported to be approximately 4,769 mg/kg ethylbenzene (Smyth et al. 1962). No short-term studies using ethylbenzene administered in food or drinking water were located.

In another oral study with rats exposed to ethylbenzene, the LD_{50} was reported to be approximately 3,500 mg/kg ethylbenzene (Wolf et al. 1956). The usefulness of these data, however, was questionable since the methodology by which this value was derived was not reported.

An oral LD_{50} value for rats is recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located describing respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or metabolic effects in humans or gastrointestinal, musculoskeletal, endocrine, dermal, ocular, body weight, or metabolic effects in animals after oral exposure to ethylbenzene.

One oral intermediate-duration study in rats was found in the literature (Wolf et al. 1956). Systemic effects described in this study are discussed below. The highest NOAEL values and all reliable LOAEL values for systemic effects in this study are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. The only animal study available in which ethylbenzene alone was administered to the animals presented no data on adverse respiratory effects in female rats orally exposed to 13.6-680 mg/kg ethylbenzene by gavage for 6 months (Wolf et al. 1956). The only parameters monitored were gross necropsy and histopathological effects. The utility of this study is limited because of poor protocol description and because the data on respiratory effects were not presented.

Cardiovascular Effects. In a single study in animals, female rats were exposed to 13.6-680 mg/kg/body weight ethylbenzene via gavage for 6 months (Wolf et al. 1956). The only parameter monitored was histopathology of the cardiac tissue. However, these data were not presented in the study. Therefore, no conclusions can be drawn.

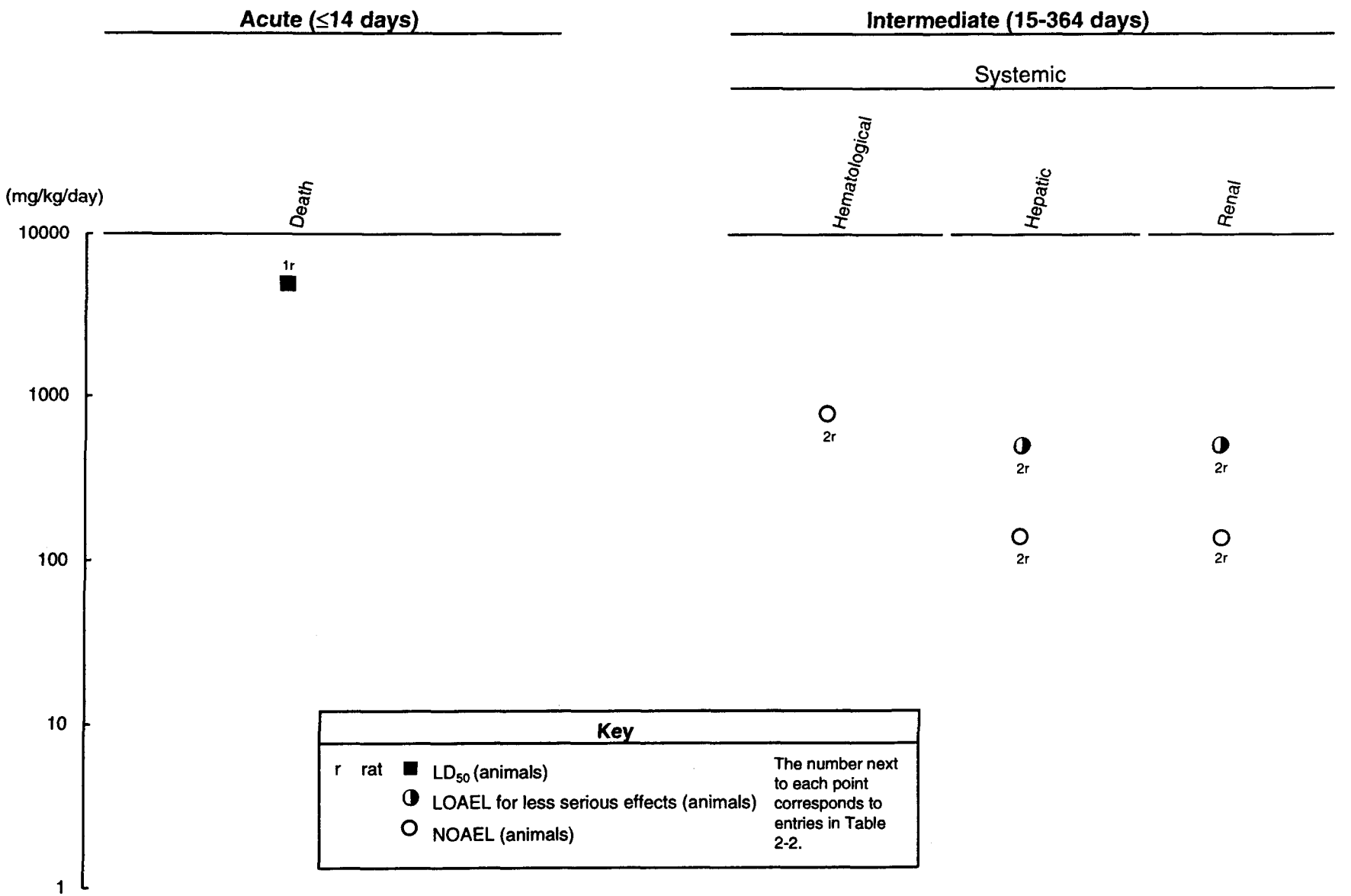
Table 2-2. Levels of Significant Exposure to Ethylbenzene - Oral

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (Carworth-Wistar)	once (G)				4769 M (LD_{50})	Smyth et al. 1962
	INTERMEDIATE EXPOSURE						
	Systemic						
2	Rat	6 mo 5 d/wk 1 x/d (GO)	Hemato	680 F			Wolf et al. 1956
			Hepatic	136 F	408 F (increased liver weight; cloudy swelling of parenchymal liver cells)		
			Renal	136 F	408 F (increased kidney weight; cloudy swelling of kidney tubular epithelium)		

[a]The number corresponds to entries in Figure 2-2.

F = female; (G) = gavage; (GO) = gavage in oil; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level

Figure 2-2. Levels of Significant Exposure to Ethylbenzene - Oral



Hematological Effects. The only animal study available reported no adverse hematological effects in female rats orally exposed to 13.6-680 mg/kg/body weight ethylbenzene by gavage for 6 months (Wolf et al. 1956). The only parameters monitored, however, were bone marrow counts and total cell counts; thus, other hematological effects might have occurred but might not have been detected. Other weaknesses of this study include a poor description of study protocol and general lack of study details (e.g., hematological data).

Hepatic Effects. In the only animal study located, female rats were administered 13.6-680 mg/kg ethylbenzene by gavage for 6 months (Wolf et al. 1956). The authors reported histopathological changes characterized by cloudy swelling of parenchymal cells of the liver and an increase in liver weight in rats administered 408 mg/kg/day. No other hepatic changes were reported. No conclusions could be drawn from these results because of serious weaknesses in the methodology and reporting of the data (e.g., no data on number of animals with hepatic effects). Furthermore, no statistical analyses were performed.

Renal Effects. The only animal study that investigated renal effects following ethylbenzene exposure involved female rats administered 13.6-680 mg/kg/body weight ethylbenzene by gavage for 6 months (Wolf et al. 1956). Histopathological changes characterized as cloudy swelling of the tubular epithelium in the kidney and an increase in kidney weight were observed at the 408 mg/kg/day dose level. No other renal changes were reported. As in hepatic effects, no conclusions could be drawn from these results because of serious weaknesses in the methodology and reporting of the data (e.g., no data on the number of animals with renal effects). Furthermore, no statistical analysis were performed.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals following oral exposure to ethylbenzene.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to ethylbenzene.

In an animal study that monitored behavioral changes, female rats were administered ethylbenzene by gavage for 6 months at concentrations ranging from 13.6 to 680 mg/kg/body weight (Wolf et al. 1956). No data on ethylbenzene-related behavioral changes were presented. No other parameters were investigated. The utility of this study is limited because the monitored behavioral changes were not reported, and the study protocol was poorly described. Given these weaknesses, no conclusions on neurological effects resulting from oral exposure to ethylbenzene can be drawn. No additional studies in animals were located regarding neurological effects following oral exposure to ethylbenzene.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to ethylbenzene.

The only available reproduction study with animals indicates that acute oral exposure to 500 or 1,000 mg/kg ethylbenzene decreases peripheral hormone levels and may block or delay the estrus cycle in female rats during the diestrus stage (Ungvary 1986). Decreased levels of hormones, including luteinizing hormone, progesterone, and 17 β-estradiol, were accompanied by uterine changes, which consisted of increased stromal tissue with dense collagen bundles and reduced lumen. No dose response was noted. The study limitations included lack of rationale for dose selection, use of only two doses, small number of test animals, and no statistical analysis of the data.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans and animals following oral exposure to ethylbenzene.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following oral exposure to ethylbenzene. Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans following oral exposure to ethylbenzene.

The carcinogenicity of ethylbenzene by the oral route has been evaluated in a chronic-duration study in Sprague-Dawley rats (Maltoni et al. 1985). A statistically significant increase in total malignant tumors was reported in females and in combined male and female groups exposed to 500 mg kg/day via gavage for 104 weeks and observed until after week 141. Evaluation of these results is difficult because no data on specific tumor type were presented. Other limitations of this study include the fact that only one dose was tested, and no information on survival was provided.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding lethal effects in humans following only dermal exposure to ethylbenzene. Matsumoto et al. (1992) reported the case of a 44-year-old man who was found unconscious in his gasoline vapor-filled car with his clothes wet with gasoline. The gasoline contained ethylbenzene among many other constituents. The patient emptied at least 18 L of gasoline into his car and was exposed to it for 10 hours or more. The patient died after 9 days of multiple organ failure.

The dermal LD_{50} in rabbits exposed to liquid ethylbenzene was calculated to be 15,433 mg/kg/body weight (Smyth et al. 1962). However, it is difficult to apply precise quantities of volatile compounds to the skin. No additional studies were located regarding death in animals following dermal exposure to ethylbenzene.

2.2.3.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, body weight, or metabolic effects in humans or animals after dermal exposure to ethylbenzene.

The systemic effects observed after dermal exposure to ethylbenzene are discussed below. The highest NOAEL values and all reliable LOAEL values for each species and duration category are recorded in Table 2-3.

Respiratory Effects. Nose and throat irritation were reported in volunteers exposed to an ethylbenzene concentration of 2,000 ppm for 1-6 minutes (Yant et al. 1930). Three volunteers exposed to 5,000 ppm reported extreme irritation of the nose, and throat.

In animals, nasal irritation was reported in guinea pigs exposed to 1,000 ppm for 3 minutes, and in guinea pigs exposed to 2,000, 5,000, and 10,000 ppm for 480, 30, and 10 minutes, respectively (Yant et al. 1930). Gross histopathology revealed congestion and edema in the lungs with an increase in the severity of damage with increased exposure concentration (dose not specified).

Respiratory effects observed in humans and animals after inhalation exposure are assumed to be due to exposure of the mucous membranes and respiratory system to ethylbenzene vapor.

Dermal Effects. No studies were located regarding dermal effects in humans following dermal exposure to ethylbenzene. Matsumoto et al. (1992) reported the case of a 44-year-old man found unconscious in his gasoline vapor-filled car with his clothes wet with gasoline containing ethylbenzene among many other constituents. The patient emptied at least 18 L of gasoline into his car and was exposed to it for 10 hours or more. He was diagnosed as suffering from chemical burns and died after 9 days due to multiple organ failure.

Liquid ethylbenzene applied directly to the skin of an unspecified number of rabbits caused irritation characterized by reddening, exfoliation, and blistering (Wolf et al. 1956). Mild dermal irritation (grade 2 on a scale of 10) was also noted in New Zealand White rabbits 24 hours after application of ethylbenzene to clipped skin (Smyth et al. 1962).

Ocular Effects. Ocular effects observed in humans and animals after inhalation exposure are assumed to be due to exposure of the mucous membranes of the eye to ethylbenzene vapor. Volunteers reported eye irritation and burning, and profuse lacrimation which gradually decreased with continued exposure to 1,000 ppm for 1-6 minutes (Yant et al. 1930). Upon entering the chamber with an ethylbenzene concentration of 2,000 or 5,000 ppm, the volunteers also experienced severe eye irritation. Cometto-Muniz

Table 2-3. Levels of Significant Exposure to Ethylbenzene - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL	LOAEL			Reference
				Less serious		Serious	
ACUTE EXPOSURE							
Death							
Rabbit (New Zealand)	24 hr					15433 M (LD_{50}) mg/kg/d	Smyth et al. 1962
Systemic							
Rabbit (New Zealand)	24 hr	Dermal		8.67 mg	(grade 4 skin irritation)		Smyth et al. 1962
INTERMEDIATE EXPOSURE							
Systemic							
Rat (F344/N)	13 wk 5 d/wk 6 hr/d	Ocular	975 ppm				NTP 1992
Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d	Ocular	975 ppm				NTP 1992

d = day(s); hr = hour(s); LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week(s)

and Cain (1995) measured eye irritation in humans after exposure to ethylbenzene vapor. Eye irritation was observed at 10,000 ppm.

Liquid ethylbenzene applied directly to the eyes of rabbits for an unspecified duration caused slight irritation of conjunctival membranes (Wolf et al. 1956) and slight cornea1 injury (Smyth et al. 1962; Wolf et al. 1956).

Irritative effects from exposure to ethylbenzene vapor have been reported in animals. Tegeris and Balster (1994) reported lacrimation and palpebral closure in CFW mice after 20 minutes of exposure to 2,000 ppm ethylbenzene. Eye irritation was observed in guinea pigs exposed to 1,000 ppm for 8 minutes, and in animals exposed to 2,000, 5,000, and 10,000 ppm for 480,30, and 10 minutes, respectively (Yant et al. 1930). After 4 days of inhalation exposure to 1,200 ppm ethylbenzene, Fischer 344 rats exhibited lacrimation (Biodynamics 1986; Cragg et al. 1989). B6C3F_1 mice and New Zealand White rabbits exhibited lacrimation after exposure to 400 ppm. After 4 weeks of exposure to 382 ppm, rats showed sporadic lacrimation, whereas mice and showed no ocular effects at 782 and 1,610 ppm, respectively (Cragg et al. 1989). No ocular effects were seen in Fischer 344/N rats and B6C3F_1 mice after a 13-week exposure to 975 ppm ethylbenzene (NTP 1992).

No studies were located regarding the following health effects in humans or animals after dermal exposure to ethylbenzene:

2.2.3.3 Immunological and Lymphoreticular Effects

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

2.3 TOXICOKINETICS

The toxicokinetics of ethylbenzene have been examined in a number of studies. There is no information that suggests that ethylbenzene is handled differently by children than by adults. No specific information was found concerning ethylbenzene concentrations in breast milk, placenta, cord blood, or amniotic fluid. However, since ethylbenzene has been found in fat tissue, it is likely to be found in breast milk.

2.3.1 Absorption

2.3.1 .1 Inhalation Exposure

Inhalation studies in humans demonstrate that ethylbenzene is rapidly and efficiently absorbed via this route. Human volunteers exposed for 8 hours to ethylbenzene at concentrations of 23-85 ppm were shown to retain 64% of the inspired vapor, with only trace amounts detected in expired air (Bardodej and Bardodejova 1970). Another inhalation study that involved humans exposed to similar levels of ethylbenzene demonstrated mean retention rates of 49%, suggesting possible variability of absorption rates among individuals (Gromiec and Piotrowski 1984).

Matsumoto et al. (1992) determined the total gasoline concentration and that of several constitutive hydrocarbons in the blood of a 44-year-old man fatally exposed to the fumes from at least 18 L of gasoline for 10 hours or more. Blood samples were collected from 2 to 7 days and analyzed by gas chromatography/ mass spectrometry (GC/MS). The estimated initial concentration of ethylbenzene in the blood was 2.6 μg/mL with a half-life of 27.5 hours. This absorption value may have been slightly overestimated, however, because possible contributions from dermal exposure were not addressed.

Fustinoni et al. (1995) conducted environmental and biological monitoring of traffic policemen in Milan exposed to airborne aromatic hydrocarbons. Concentration values of ethylbenzene in air by passive diffusion personal samplers expressed as time-weighted average (TWA) in four subjects a day for 10 days showed mean outdoor concentration (n=20) of 37 mg/m^3 (range, 11-87 mg/m^3 or 2.5-20 ppm) as significantly higher than the mean indoor concentration (n=19) of 21 mg/m^3 (range, 2-40 mg/m^3 or 0.46-9.2 ppm). Blood concentrations of ethylbenzene found in non-smoking policemen before and after workshift showed no significant differences between outdoor (n=16; 158 ng/L before shift, 184 ng/L after shift) and indoor (n=14; 140 ng/L before shift, 162 ng/L after shift) groups and between before and after

workshift values for ethylbenzene for either indoor or outdoor exposure. No significant differences were found in blood concentrations obtained from non-smokers (n=30) and smokers (n=9) before (150 ng/L versus 197 ng/L) and after (174 ngL versus 222 ng/L) workshift.

Holz et al. (1995) determined low-level exposure to ethylbenzene and its effect on peripheral lymphocytes in workers in a styrene production plant. The concentration of ethylbenzene for exposed workers determined from active air sampling at four different locations (oven house, production control, storage facility, and distillation area) ranged from 365 to 2,340 μg/m^3 (84.1-538.9 pim). Measurements performed at the pump house showed ethylbenzene concentration levels >4,000 μg/m^3 (921 ppm), which exceeded the detection limit of the sampling device. Ethylbenzene concentration levels for control workers ranged from 145 to 290 μg/m^3 (33.4-66.8 ppm). Presence of metabolites in urine sampled after shift in the exposed workers indicated absorption of ethylbenzene had occurred.

In a study of chronic-duration exposure of factory workers at low levels of 2.1 ppm (geometric mean) or 2.3 ppm (arithmetic mean) ethylbenzene (maximum at 5 ppm), solvent concentrations in both whole-blood and serum samples collected at the end of shifts correlated significantly with the TWA concentrations of occupational exposure to ethylbenzene (Kawai et al. 1992).

Inhalation studies in animals exposed to ethylbenzene showed results similar to those found in humans. Harlan-Wistar rats rapidly absorbed radiolabeled ethylbenzene during respiration, with a retention rate of 44% (Chin et al. 1980b). This absorption value may have been slightly overestimated, however, because possible contributions from dermal exposure were not addressed. These studies did not correlate measured toxic effects with kinetic observations. No studies describing factors affecting absorption of ethylbenzene following inhalation exposure were available.

2.3.1.2 Oral Exposure

No studies were located regarding the absorption of ethylbenzene in humans following oral exposure. Studies in animals, however, indicate that ethylbenzene is quickly and effectively absorbed by this route. Recovery of ethylbenzene metabolites in the urine of rabbits administered a single dose of 593 mg/kg was between 72 and 92% of the administered dose 24 hours following exposure (El Masri et al. 1956). Similarly, 84% of the radioactivity from a single oral dose of 30 mg/kg ethylbenzene administered to female Wistar rats was recovered within 48 hours (Climie et al. 1983).

2.3.1.3 Dermal Exposure

Studies in humans dermally exposed to liquid ethylbenzene demonstrate rapid absorption through the skin, but absorption of ethylbenzene vapors through the skin appears to be minimal (Dutkiewicz and Tyras 1967; Gromiec and Piotrowski 1984). Absorption rates of 24-33 mg/cm^2/hour and 0.11-0.23 mg/cm^2/hour have been measured for male subjects exposed to liquid ethylbenzene and ethylbenzene from aqueous solutions, respectively (Dutkiewicz and Tyras 1967). The average amounts of ethylbenzene absorbed after volunteers immersed 1 hand for up to 2 hours in an aqueous solution of 112 or 156 mg/L ethylbenzene were 39.2 and 70.7 mg ethylbenzene, respectively. These results indicate that skin absorption could be a major route of uptake of liquid ethylbenzene or ethylbenzene in water. In contrast, ethylbenzene metabolite levels in urine following dermal exposure of human volunteers to ethylbenzene vapors did not differ from values taken prior to exposure, indicating minimal, if any, dermal absorption of ethylbenzene vapors (Gromiec and Piotrowski 1984).

Matsumoto et al. (1992) determined the total concentration of gasoline and several constitutive hydrocarbons in the blood of a 44-year-old man fatally exposed to the gasoline fumes and gasoline-soaked clothing and skin from at least 18 L of gasoline for 10 hours or more. Blood sample were collected from 2 to 7 days and analyzed by gas chromatography/mass spectrometry. The estimated initial concentration of ethylbenzene in the blood was 2.6 μg/mL with a half-life of 27.5 hours. The relative contributions of both inhalation and dermal absorption were not determined

The older, limited animal data on dermal absorption of liquid ethylbenzene are inconclusive. An unspecified number of rabbits dermally exposed to liquid ethylbenzene for 2-4 weeks demonstrated no apparent absorption through the skin (Wolf et al. 1956). However, this study is of limited value because absorption was measured only by overt signs of acute toxicity (e.g., gross appearance, behavior, and changes in body weight). The penetration rates of liquid ethylbenzene have been examined in excised rat skin (Tsuruta 1982). The penetration rates of ethylbenzene following 3-, 4-, and 5-hour exposure durations in rat skin were calculated to be 0.002,0.003, and 0.004 mg/cm^2/hour; these rates are substantially lower than the rate of dermal absorption determined for humans. This might be attributed to differences between *in vitro* and *in vivo* testing and/or differences in rat versus human skin.

Two more recent studies provide more definitive data on the *in vivo* absorption of ethylbenzene through rodent skin (Morgan et al. 1991; Susten et al. 1990). Morgan et al. (1991) investigated dermal absorption

of pure and dilute aqueous solutions of ethylbenzene in male Fischer 344 rats. Rats were exposed to either neat (99% purity), saturated (134 μg/mL), 2/3 saturated (84 μg/mL), or l/3 saturated (47 μg/mL) aqueous ethylbenzene for 24 hours. Blood samples were obtained from each rat via indwelling jugular catheters before addition of test chemical and after exposure for 0.5, 1, 2,4, 8, 12, and 24 hours. The concentration of ethylbenzene in the blood was determined by gas chromatography. Peak blood level during exposure to neat ethylbenzene was reported at 5.6 μg/mL attained after 1 hour of exposure, which decreased during the remainder of the exposure period. The concentration of ethylbenzene in the blood was highest after exposure to saturated aqueous solutions, followed by the 2/3 and 1/3 saturated solutions. The volume of ethylbenzene absorbed from the exposure cells after 24-hour dermal exposures was 0.24, 0.20,0.18, and 0.17 mL for neat, saturated, 2/3 saturated and 1/3 saturated, respectively. The volume of water absorbed by the animals in a 24-hour period when exposure cells contained only distilled water was 0.18 mL. This study suggests that in rats, significant amounts of ethylbenzene can be absorbed through the skin not only from the neat compound but also from an aqueous solution.

Susten et al. (1990) conducted in viva percutaneous absorption studies of ethylbenzene in Hairless mice. Results showed total absorption (sums of radioactivity found in the excreta, carcass, skin application site, and expired breath) was 3.4% of the nominal dose. The total percentage recovered (includes wipe of skin area, ethylbenzene 0.03%) was 95.2%. The amount of ethylbenzene absorbed at an estimated contact time of 5 minutes was 148.55 μg with an absorption rate of 37 μg cmm^{-2} min^{-1}.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

In humans exposed for 2 hours to a mixture of industrial xylene containing 40.4% ethylbenzene, the estimated solvent retention in adipose tissue was 5% of the total uptake (Engstrom and Bjurstrom 1978). Since there was no indication of differences in turnover rates of chemicals within the mixture, it is likely that the retention of ethylbenzene in adipose tissue was approximately 2% of the total uptake. No studies were located concerning the distribution of ethylbenzene in humans following exposure to ethylbenzene alone. However, studies by Pierce et al. (1996) suggest that *in vitro,* the partitioning of ethylbenzene from air into human adipose tissue is similar to that observed in rats.

In rats, the concentrations of ethylbenzene in perirenal adipose tissue were reported to increase, although not linearly, with increasing concentrations of ethylbenzene (Engstrom et al. 1985) and in a mixture of solvent vapors containing ethylbenzene (Elovaara et al. 1982). The less-than-linear increase of ethylbenzene in adipose tissue with increasing dose was partially attributed to the induction of drug-metabolizing enzymes occurring with increasing exposure concentrations, altered blood flow to adipose tissue, changes in lung excretion, and changes in the distribution of ethylbenzene in different tissues. Ethylbenzene was shown to be efficiently distributed throughout the body in rats following inhalation exposure to radiolabeled ethylbenzene (Chin et al. 1980b). The highest amounts of radioactivity in tissues 42 hours after exposure to 230 ppm ethylbenzene for 6 hours were found in the carcass, liver, and gastrointestinal tract, with lower amounts detected in the adipose tissue.

2.3.2.2 Oral Exposure

No studies were located regarding distribution of ethylbenzene in humans following oral exposure. Data on the distribution of radiolabeled ethylbenzene hydroperoxide 1, 3, and 8 days after oral administration to rats were provided by Climie et al. (1983). Tissue residues were highest in the intestine, liver, kidney, and fat (0.53, 0.2, 0.21, and 0.27 μg/g tissue, respectively) 1 day after exposure and decreased to trace amounts (less than 0.05 μg/g tissue) in all tissues monitored (carcass, skin, muscle, and blood) 8 days after exposure. However, differences in the physical and chemical properties of ethylbenzene and ethylbenzene hydroperoxide (e.g., the potential of ethylbenzene hydroperoxide to generate free radicals) may affect distribution. No distribution data on radiolabeled ethylbenzene were provided.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans following dermal exposure to ethylbenzene.

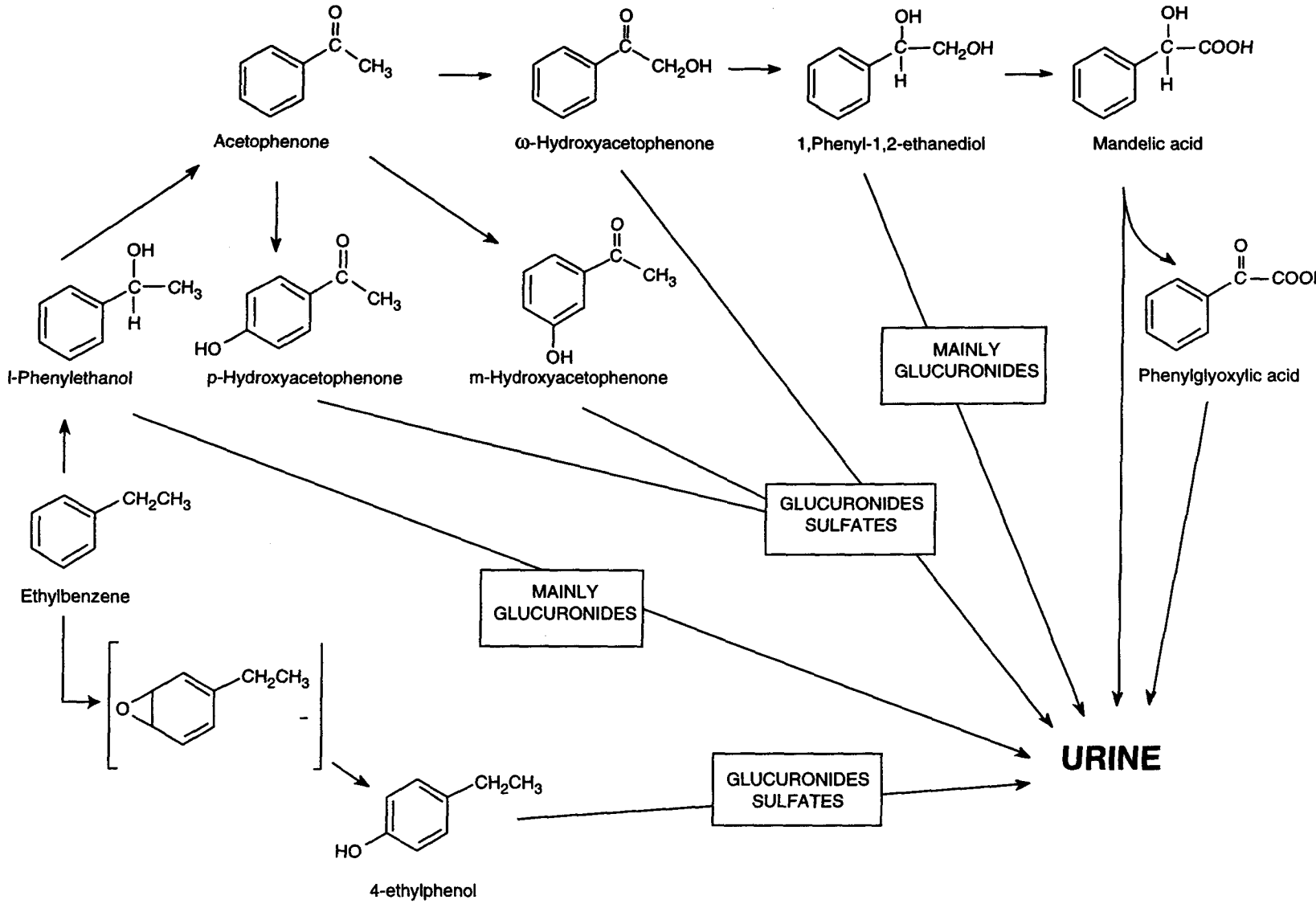
Susten et al. (1990) conducted *in vivo* percutaneous absorption studies of ethylbenzene in Hairless mice. Results showed that total absorption (sums of radioactivity found in the excreta, carcass, skin application site and expired breath) was 3.4% of the nominal dose. The percentages of absorbed doses following dermal application of [^{14}C]-ethylbenzene were: carcass, 15.5%; application site, 4.5%; expired breath, 14.3%; and excreta, 65.5%.

2.3.3 Metabolism

The metabolism of ethylbenzene has been studied in humans and other mammalian species. The data demonstrate that ethylbenzene is metabolized mainly through hydroxylation and then through conjugation reactions from which numerous metabolites have been isolated. Figure 2-3 summarizes the proposed metabolic pathway for ethylbenzene in humans (Engstrom et al. 1984). The major urinary metabolites have been identified (Kiese and Lenk 1974; Sullivan et al. 1976). Comparisons of in vitro data with data from intact animals indicate that liver microsomal enzymes may participate in ethylbenzene hydroxylation (McMahon and Sullivan 1966; McMahon et al. 1969), and evidence suggests that the adrenal cortex may be a major site of extra-hepatic ethylbenzene metabolism (Greiner et al. 1976). No significant differences in metabolism between oral and inhalation routes were reported in humans or animals. The metabolism of ethylbenzene has been found to vary with species, sex, and nutritional status. These differences are described below.

In humans exposed via inhalation, the major metabolites of ethylbenzene are mandelic acid (approximately 64-71%) and phenylglyoxylic acid (approximately 19-25 %) (Bardodej and Bardodejova 1970; Engstrom et al. 1984). Based on data from human, animal, and *in vitro* studies, the metabolic pathway for ethylbenzene in humans was proposed (Engstrom et al. 1984). This pathway is shown in Figure 2-3. Evidence indicates that the initial step in this metabolic pathway is oxidation (hydroxylation) of the side chain of ethylbenzene to produce 1-phenylethanol. Microsomal preparations from rat liver have shown that the oxidation of ethylbenzene proceeds with the incorporation of atmospheric oxygen, as opposed to oxygen from water molecules (McMahon et al. 1969). Flipovic et al. (1992) have shown that cytochrome $P\text{-}450_{(cam)}$ from *Pseudomonas putidu* provides a useful metabolic model for ethylbenzene hydroxylation, converting ethylbenzene to 1-phenylethanol at 98%. 1-Phenylethanol is conjugated to glucuronide, which then is either excreted or converted to subsequent metabolites. Oxidation of 1-phenylethanol yields acetophenone, which is both excreted in the urine as a minor metabolite and further transformed. Continued oxidation of the side chain leads to the sequential formation of 2-hydroxyacetophenone, 1 -phenyl- 1,2-ethanediol mandelic acid, and phenylglyoxylic acid. Minor pathways (e.g., ring hydroxylation) include glucuronide and sulfate conjugation with hydroxylated derivatives to form glucuronides and sulfates that are excreted in the urine. Analysis of urine from humans exposed to ethylbenzene via the inhalation route showed that approximately 70 and 25% of the retained dose of ethylbenzene is excreted as mandelic acid and phenylglyoxylic acid, respectively (Bardodej and Bardodejova 1970; Engstrom et al. 1984). Additional

Figure 2-3. Metabolic Scheme for Ethylbenzene in Humans



metabolites detected in human urine include 1-phenylethanol(4%), p-hydroxyacetophenone (2.6%), m-hydroxyacetophenone (1.6%), and trace amounts of 1-phenyl- 1,2-ethanediol, acetophenone, 2-hydroxy-acetophenone, and 4-ethylphenol. Following dermal exposure of humans, however, excretion of mandelic acid was shown to be only 4.6% of the absorbed dose (Dutkiewicz and Tyras 1967), which may indicate differences in the metabolic fate between inhalation and dermal exposure routes. However, the small percentage of absorbed dose accounted for limits the interpretation. No animal data were located which could confirm these metabolic differences following dermal exposure. Generally, ethylbenzene metabolites and intermediates are thought to be only slightly toxic, since no adverse effects from human experimental exposure have been reported (Bardodej and Bardodejova 1970).

Qualitative and quantitative differences in the biotransformation of ethylbenzene in animals as compared to humans have been reported (Bakke and Scheline 1970; Climie et al. 1983; El Masri et al. 1956; Engstrom 1984; Engstrom et al. 1985; Smith et al. 1954a, 1954b; Sollenberg et al. 1985). The major metabolites of ethylbenzene differ from species to species, and different percentages of the metabolites are seen in different species. The principal metabolic pathway in rats is believed to begin with oxidation (hydroxylation) of the side chain as in humans (Climie et al. 1983; Engstrom 1984; Engstrom et al. 1985; Smith et al. 1954a). In rats exposed by inhalation or orally to ethylbenzene, the major metabolites were identified as hippuric and benzoic acids (approximately 38%), I-phenylethanol (approximately 25%), and mandelic acid (approximately 15-23%), with phenylglyoxylic acid making up only 10% of the metabolites (Climie et al. 1983; Engstrom 1984; Engstrom et al. 1985). Both *in vivo* studies using rats and *in vitro* studies using rat liver microsomes showed that 4-ethylphenol was also produced from ethylbenzene, perhaps by rearrangement of corresponding arene oxides (Bakke and Scheline 1970; Kaubisch et al. 1972). Kaubisch et al. (1972) also showed that 2-hydroxyethylbenzene was produced from ethylbenzene *in vitro* in the presence of rat liver microsomes. The level of ethylbenzene exposure was shown to affect the metabolic pattern. This was thought to be due either to selective enzymatic induction in the biotransformation of ethylbenzene or to delayed excretion of certain metabolites with increasing doses.

Further clarification of ethylbenzene metabolic pathways was provided by Sullivan et al. (1976). Using intraperitoneally dosed rats, the authors demonstrated that the conversion of 1-phenylethanol to mandelic acid initially involves oxidation to acetophenone. Acetophenone was considered to be the precursor of mandelic acid, benzoylformic acid, and benzoic acid. A similar study in which rabbits were intraperitoneally injected with a single dose of 250 mg ethylbenzene/kg body weight was conducted by Kiese and Lenk (1974). This study showed that between 1% and 10% of the dose was excreted as

1 -phenylethanol in the urine and less than 1% was excreted in the urine as 2-hydroxyacetophenone, *p*-hydroxyacetophenone, and *m*-hydroxyacetophenone.

Rabbits given an oral dose of ethylbenzene showed the major metabolic pathway to be hydroxylation of the a-carbon to 1-phenylethanol, which is oxidized further to a number of intermediates and metabolites (El Masri et al. 1956; Smith et al. 1954a). Many of these intermediates are subsequently conjugated to glucuronides and sulfates and excreted. In rabbits, the most important metabolite is hippuric acid, which is probably formed by oxidative decarboxylation of phenylglyoxylic acid (El Masri et al. 1958). Oxidation of the methyl group of ethylbenzene was also shown to occur, as evidenced by the presence of phenaceturic acid in the urine. A slight increase in the excretion of thioether suggests that glutathione conjugation may also play a minor role.

The nutritional status of animals was demonstrated to have a marked effect on ethylbenzene metabolism in rats (Nakajima and Sato 1979). The in vitro metabolic activity of liver microsomal enzymes on ethylbenzene was shown to be significantly enhanced in fasted rats despite a marked loss of liver weight. No significant increases in the microsomal protein and cytochrome P-450 contents were detected in fasted rats compared with fed rats. In addition, the metabolic rate in fasted males was significantly higher than in fasted females, but the difference in rates decreased following food deprivation for 3 days. These results suggest possible sex differences in the rate of ethylbenzene metabolism. However, it is not known if such differences exist in the normally fed rats.

Metabolism of ethylbenzene has not been studied in children or immature animals. However, some members of two of the enzyme superfamilies involved in conjugation of phase I ethylbenzene metabolites are known to be developmentally regulated. In humans, UDP glucuronosyltransferase activity does not reach adult levels until about 6-18 months of age, although the development of this activity is isoform specific. Activity of sulfotransferases seems to develop earlier, although again, it is isoform specific. The activity of some sulfotransferase isoforms may even be greater during infancy and early childhood than in adults (Leeder and Kearns 1997).

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Excretion of ethylbenzene has been studied in humans and in a number of animal species. Ethylbenzene has been shown to be rapidly metabolized and then eliminated from the body, primarily as urinary metabolites. The major metabolic products have been previously described in Section 2.3.3. Elimination of ethylbenzene has been studied in human volunteers exposed by inhalation (Bardodej and Bardodejova 1970; Dutkiewicz and Tyras 1967; Engstrom and Bjurstrom 1978; Gromiec and Piotrowski 1984; Yamasaki 1984), or humans exposed by inhalation in the occupational setting (Holz et al. 1995; Kawai et al. 1991, 1992; Ogata and Taguchi 1988). The elimination of the ethylbenzene metabolite, mandelic acid, was reported to be rapid, with the acid detected in the first urine sample following the initiation of an g-hour inhalation exposure to 0, 4, 8, 18, 35, or 46 ppm ethylbenzene (Gromiec and Piotrowski 1984). Elimination of mandelic acid was reported to be biphasic, with half-lives of 3.1 hours for the rapid phase and 25 hours for the slow phase (Gromiec and Piotrowski 1984). During the g-hour exposure, 23% of the retained ethylbenzene was eliminated in the urine, and 14 hours following termination of exposure an additional 44% of the retained ethylbenzene was eliminated. The highest excretion rate of urinary metabolites in humans exposed to ethylbenzene by inhalation occurred 6-10 hours after the beginning of exposure (Gromiec and Piotrowski 1984; Yamasaki 1984). The metabolic efficiency was reported to be independent of the exposure dose.

Occupational studies have also been conducted to determine excretion and elimination of ethylbenzene and its metabolites after inhalation exposure. Holz et al. (1995) determined low-level exposure to ethylbenzene and its effect on peripheral lymphocytes in workers in a styrene production plant. The concentration of ethylbenzene for exposed workers determined from active air sampling at four different locations (oven house, production control, storage facility, and distillation area) ranged from 365 to 2,340 $\mu g/m^3$ (84-539 ppm). Measurements performed at the pump house showed ethylbenzene concentration levels >4,000 $\mu g/m^3$ (921 ppm) which exceeded the detection limit of the sampling device. Ethylbenzene concentration levels for control workers ranged from 145 to 290 $\mu g/m^3$ (33.4-66.8 ppm). Metabolite concentrations in urine sampled after shift in the exposed workers showed significantly higher exposure to ethylbenzene (mandelic acid, 43.9 mg/g creatinine $p<0.001$; phenylglyoxylic acid, 22.3 mg/g creatinine <0.05) compared to after-shift urine samples from non-exposed workers (mandelic acid, 4.3 mg/g

creatinine; phenylglyoxylic acid, 0.5 mg/g creatinine). Urine samples compared before shift showed significant exposure of workers to ethylbenzene (mandelic acid, 13.3 mg/g creatinine $p<0.001$; phenylglyoxylic acid, 10.7 mg/g creatinine $p=0.006$) compared to controls (mandelic acid, 5.5 mg/g creatinine; phenylglyoxylic acid, 2.8 mg/g creatinine).

Kawai et al. (199 1) determined urinary metabolites after exposure of metal workers to a solvent mixture containing toluene, mixed xylenes, and ethylbenzene. The employees worked on dip-coated metal parts with rust-resistant paint in which technical grade xylene mixture was used as the sole solvent. The workers wore protective gloves but did not wear masks. Vapor exposure from the solvent mixture contained mixed xylene, toluene, and ethylbenzene. The TWA concentration of ethylbenzene in breathing-zone air of the 121 workers during the shift was 0.9 ppm (geometric mean vapor concentration); maximum value observed was 11.4 ppm. The excretion of ethylbenzene metabolites, mandelic acid and phenylglyoxylic acid, showed geometric mean concentrations of 13.7 (maximum 52 ppm) and 8 ppm (maximum 128 ppm), respectively. The correlation of ethylbenzene exposure with phenylglyoxylic acid excretion was statistically insignificant ($p>0.005$). The correlation of ethylbenzene exposure with mandelic acid excretion was significant ($p<0.001$); both the correlation coefficient and the slope of the regression line were small. Kawai et al. (1991) reported that technical difficulties were encountered in the analysis of urine for mandelic acid and that low ethylbenzene exposure made accurate quantification difficult. In a study of chronic-duration exposure at lower levels of 2.1 ppm (geometric mean) or 2.3 ppm (arithmetic mean) with a maximum at 5 ppm, no significant correlation was observed in the relation of ethylbenzene with its metabolites, phenylglyoxylic acid and mandelic acid (Kawai et al. 1992).

Ogata and Taguchi (1988) determined urinary metabolites after toluene, ethylbenzene, and mixed xylene exposure of paint-factory workers. The recoveries of mandelic acid, hippuric acid, o-methylhippuric acid (*o*-MHA), m-methylhippuric acid (m-MHA) and creatinine added to urine (n=5) ranged from 100 to 101.6, 98.9-100.6, 99-99.9, 97.2-99.9, and 98-99.3%, respectively, in exposed workers. No mandelic acid or MHAs were detected in the urine of 32 unexposed subjects examined.

In animals, elimination of ethylbenzene metabolites following inhalation exposure is rapid and occurs primarily via urinary metabolites (Chin et al. 1980a, 1980b; Engstrom 1984; Engstrom et al. 1985) and to a much lesser degree via the feces and expired carbon dioxide (Chin et al. 1980b). Rats exposed to 230 ppm radiolabeled ethylbenzene for 6 hours via inhalation excreted virtually all of the radioactivity within 24 hours after the onset of exposure (Chin et al. 1980a, 1980b). Ninety-one percent of the

radioactivity was recovered, primarily in the form of urinary metabolites. In a similar inhalation experiment using rats exposed to 300 or 600 ppm, urinary excretion was reported to be 83% and 59% of the absorbed dose within 48 hours after the onset of exposure, with 13% eliminated during the first 6 hours of exposure (Engstrom 1984).

Quantitative differences between species in the percentages of metabolites excreted in the urine were also reported by Chin et al. (1980a). In this report, urinary metabolites in dogs and rats exposed to ethylbenzene by inhalation were studied. Although similarities in the types of metabolites recovered following inhalation exposure were reported, quantitative differences, albeit minor ones, were noted in the ratio of metabolites present in the urine. These results were attributed to differences in metabolism between dogs and rats.

2.3.4.2 Oral Exposure

No studies were located regarding the excretion of ethylbenzene metabolites in humans following oral exposure to ethylbenzene.

Elimination of ethylbenzene and its metabolites in animals after oral exposure has been shown to be similar to that following inhalation exposure. Female rats administered a single oral dose of 30 mg radiolabeled ethylbenzene/kg/body weight showed very rapid elimination, mostly in the urine (Climie et al. 1983). Eighty-two percent of the radioactivity was detected in the urine, while 1.5% was detected in the feces. The major metabolites were mandelic acid (23%) and hippuric acid (34%), with 1-phenylethyl glucuronide detected as a minor metabolite. Relatively minor metabolites (e.g., 4-ethylphenol, 2-phenylethanol, 1-phenylethanol) were shown to be excreted in the urine of male rats exposed to a single oral dose of 100 mg/kg ethylbenzene administered by gavage in oil (Bakke and Scheline 1970). No data on the major metabolites were provided in this study.

In a similar study in which male rats were given single oral doses of 350 mg/kg/body weight ethylbenzene, the excretion of mandelic acid and phenylglyoxylic acid was detected in the first urine sample after exposures. Peak concentration was reached within 17 hours, and ethylbenzene was virtually eliminated 48 hours following the onset of exposure (Sollenberg et al. 1985).

As in inhalation experiments, quantitative and qualitative differences between species were shown to exist in the percentages of metabolites excreted in the urine. Rabbits orally exposed to ethylbenzene excreted large amounts of glucuronide conjugates in the urine (El Masri et al. 1956; Smith et al. 1954a, 1954b) instead of mandelic acid, hippuric acid, and phenylglyoxylic acid, which are the major metabolites in rats (see above). Glucuronide conjugates accounted for 32% of the administered dose, with mandelic acid making up only 2% of the administered dose (El Masri et al. 1956). These results were confirmed in a study by Smith et al. (1954a, 1954b), who detected 32% of a single oral dose of ethylbenzene (433 mg/kg) administered to rabbits as glucuronide conjugates excreted in the urine.

2.3.4.3 Dermal Exposure

In humans, the pattern of excretion of ethylbenzene metabolite following dermal exposure has been shown to differ significantly from the pattern in which humans have been exposed by inhalation. Excretion of mandelic acid in humans dermally exposed to ethylbenzene was only 4.6% of the absorbed ethylbenzene (Dutkiewicz and Tyras 1967). Interpretation is difficult due to the small percentage of absorbed dose accounted for. No ethylbenzene was reported to be excreted in exhaled air. No further details on the excretion patterns were provided.

Susten et al. (1990) conducted *in vivo* percutaneous absorption studies of ethylbenzene in Hairless mice. Results showed total absorption (sums of radioactivity found in the excreta, carcass, skin application site, and expired breath) was 3.4% of the nominal dose. The absorbed doses collected in expired breath during the first 15 minutes of ethylbenzene application was 9.3%. The percentage of absorbed doses following dermal application of [^{14}C]-ethylbenzene are as follows: in the carcass, 15.5%; in the application site, 4.5%; expired breath, 14.3%; and excreta, 65.5%.

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based

pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites)

based on the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model.

If PBPK models for ethylbenzene exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

The only PBPK model for ethylbenzene found in the literature is discussed below.

2.3.5.1 Summary of PBPK Models.

One PBPK model for ethylbenzene was found in the literature (Shatkin and Brown 1991). The model describes the pharmacokinetics of the dermal route of exposure to ethylbenzene in aqueous solution. The model was able to predict 94% of experimental data in humans under the same conditions.. Comparisons of dermal absorption versus inhalation and ingestion were made. This model contained no factors for children, fetuses, pregnant women, infants, or lactating women.

2.3.5.2 Ethylbenzene PBPK Model Comparison.

Since only one model was found, no comparisons can be made.

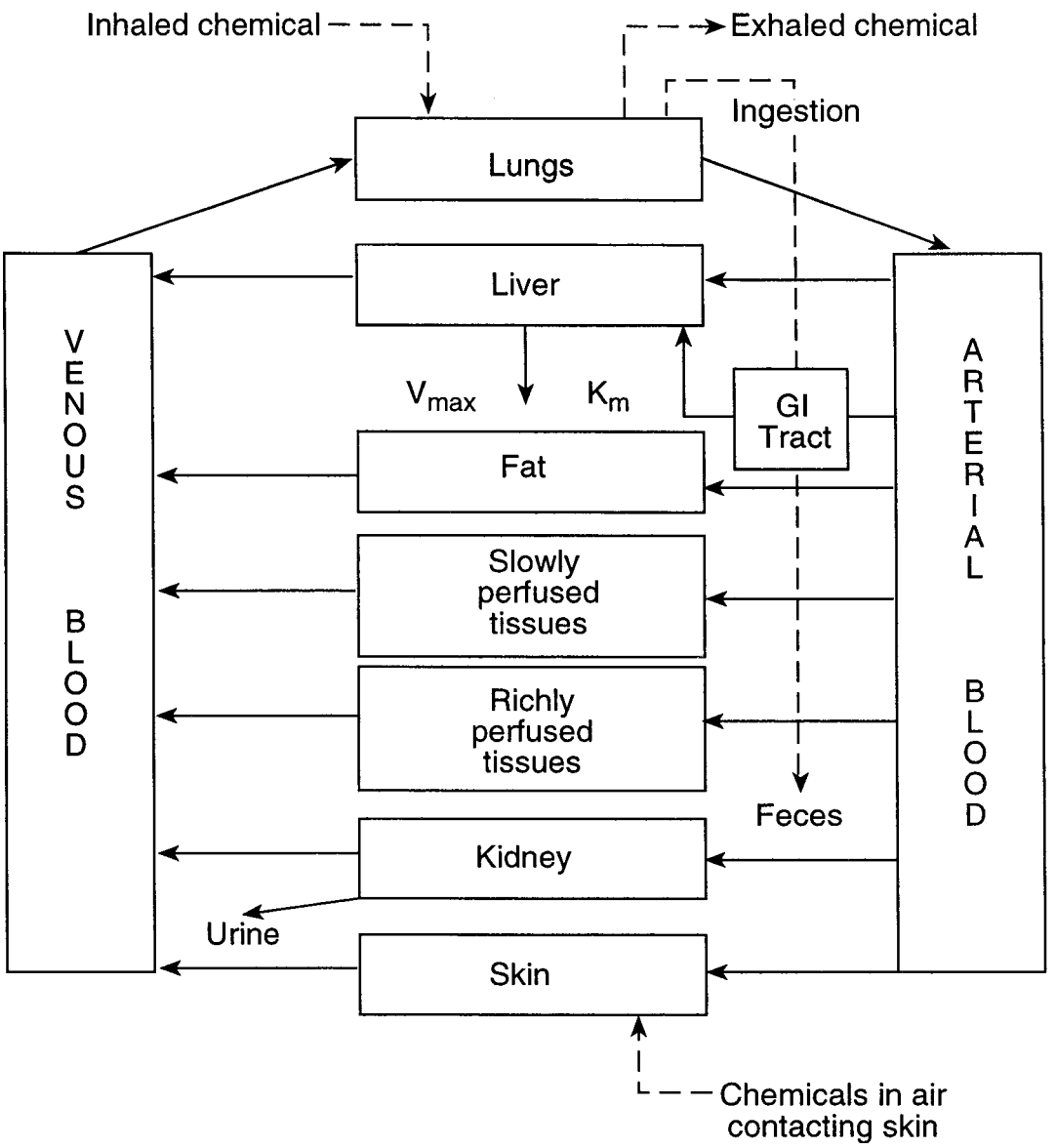
2.3.5.3 Discussion of Models.

The Shatkin and Brown Model.

Shatkin and Brown (1991) described a kinetic model of dermal absorption of several nonpolar organic nonelectrolytes in dilute aqueous solution, one of which was ethylbenzene.

Risk assessment. The authors state that the model has potentially useful applications for risk assessment if used within its limitations. The model was able to predict 94% of the experimental results with humans under the same conditions. In the case of ethylbenzene, the prediction was accurate enough to allow the authors to suggest that dermal absorption of some volatile organic chemicals from aqueous

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

solutions may be significant, and that the risk of such exposure should receive attention from the regulatory agencies. The predictions made for ethylbenzene absorption with the Shatkin and Brown (1991) model suggest that the model may be useful in estimating absorption of this compound from aqueous media through bathing, swimming, and other activities that may bring people in contact with ethylbenzenecontaminated
water.

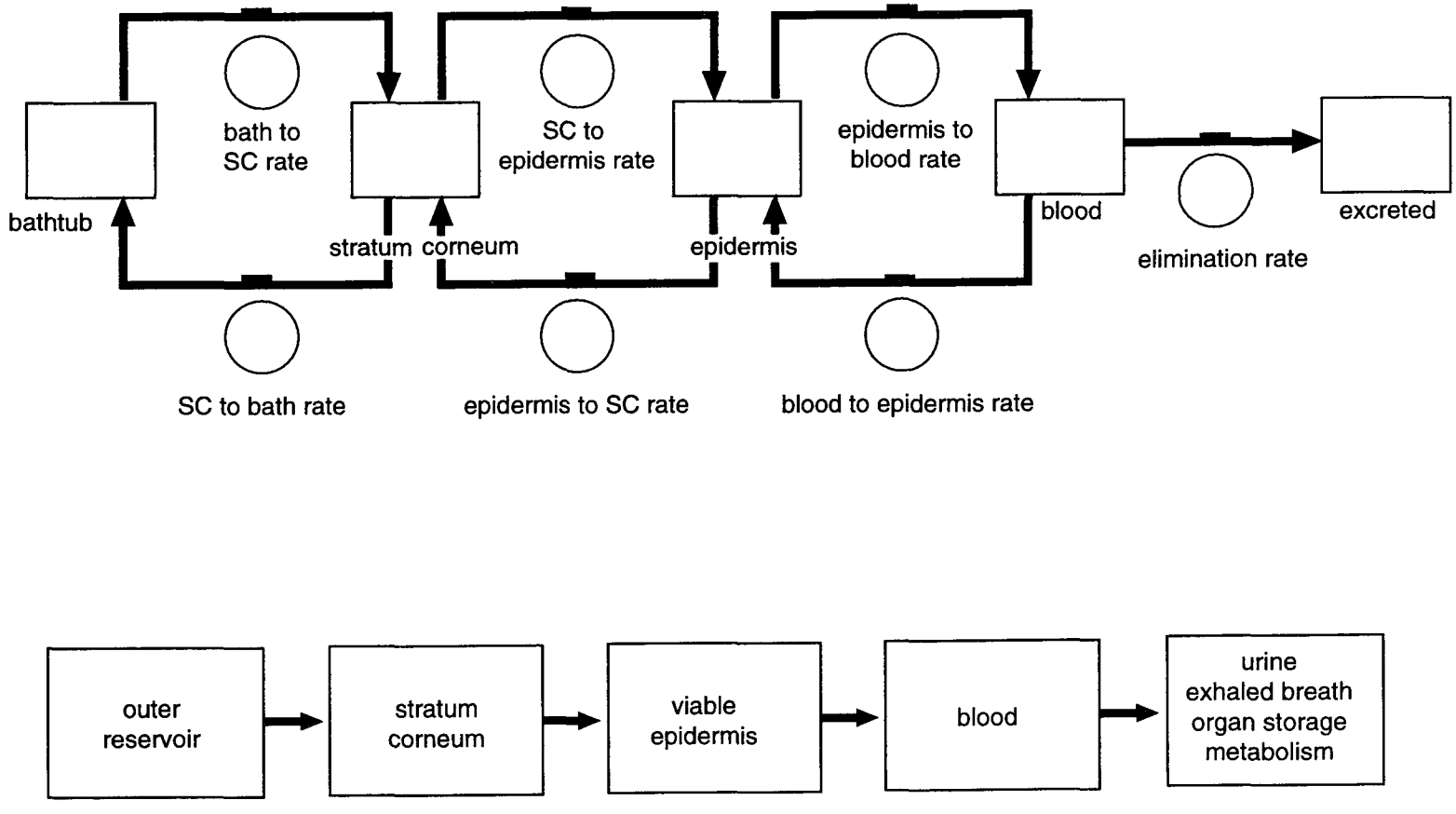
Description of the model. Shatkin and Brown (1991) presented their model both with a traditional compartmental diagram, and a scheme indicating the physiological significance of the model (Figure 2-5). Three body compartments were represented in the traditional model: stratum corneum, viable epidermis, and blood. Molecules of the solvent were assumed to diffuse through fully hydrated stratum corneum and viable epidermis in a dissolved state by purely passive means, with passage through the stratum corneum being the rate-limiting step. A uniform thickness of 40 μm was assumed for the stratum corneum, with adjustments for different body parts. Immersion of the hand, or of the full body was assumed for the predicted models. The viable epidermis was assumed to be 200 μm, although the thickness was varied to test the outcome of the model.

Blood was the third kinetic compartment used in the traditional model. No distinction was made between blood in the dermal circulation and blood in the systemic circulation. Transfer of the chemical from the epidermis into the blood was considered to be proportional to the amount of chemical in the epidermis, the epidermal blood flow, and the relative solubility of the chemical in the two compartments (epidermis/blood partition coefficient). Blood and epidermis were considered to be in equilibrium. The change in the amount of chemical in the epidermis was considered to be dependent upon the rate of entry from, and removal to the stratum comeum, removal into the blood, and reentry from the blood.

The overall elimination rate of the chemical from the blood includes excretion via inhalation, urinary filtration, metabolism, and disposition in other body compartments. First-order kinetic behavior was assumed for all compartments.

The model was conceptualized based on physiological relationships, as shown in Figure 2-5. The model was then entered into a computer program, where the conceptual relationships between the compartments defined in Figure 2-5 are described mathematically with parameters shown in Table 2-4.

Figure 2-5. Schematic Representation of the Model of Dermal Absorption



Source: Shatkin and Brown 1991

Table 2-4. Parameters Used in the Shatkin and Brown PBPK Model of Dermal Absorption of Ethylbenzene

Parameter[a]	Value	Reference
Stratum corneum/water partition coefficient (K_m)	NG	Calculated from Roberts et al. 1975
Stratum corneum diffusion coefficient (D_{sc})	NG	Calculated from Guy and Maibach 1984
Skin surface (adult hands and forearms) (adult body)	320 cm^2 NG	Dutkiewicz and Tyras 1967, 1968 Guy and Maibach 1984
Skin surface (infant)	1,900 cm^2	Guy and Maibach 1984
Epidermis diffusion coefficient (D_e)	$3.6x10^{-4}$ cm^2/min	Scheuplein 1969, 1976
Stratum corneum thickness (H_{sc})	0.004 cm	Blank and Scheuplein 1969
Epidermis thickness (H_e)	0.02–0.1 cm	Blank and McAuliffe 1985; Blank and Scheuplein 1969; Guy et al. 1982
Epidermal blood flow (F_{eb}) (adult at rest)	280 mL/min–m^2	Wade et al. 1962
Epidermal blood flow (F_{eb}) (adult, heavy exercise)	4,000 mL/min–m^2	Rowell 1986
Epidermis/blood partition coefficient (K_{eb})	2.75	Shatkin and Brown 1991
Stratum corneum/epidermis partition coefficient ($K_{sc/e}$)	NG	Shatkin and Brown 1991
Blood volume (V_b) (adults)	5,000 mL	Shatkin and Brown 1991
Blood volume (V_b) (infants)	693 mL	Shatkin and Brown 1991
Fat in blood	0.7–0.9%	Brown and Hattis 1989
Fat in stratum corneum	3–6%	Raykar et al. 1988
Fat in epidermis	2–2.5%	Scheuplein 1976
Elimination rate constant (K_e)	0.1 min^{-1}	Hagemann 1979
Octanol/water partition coefficient (K_{ow})	2,230	Published value (reference not cited by authors)

[a]Taken from Shatkin and Brown 1991. All parameters used were either taken from published experimental work of others or calculated from previously reported mathematical relationships.

NG = value not given

In order to test the model, simulations were run using the conditions as in the experiments of Dutkiewicz and Tyras (1967, 1968) (i.e., 1-hour immersion of adult male hands in an aqueous solution). The model indicated that the skin compartments reach steady-state more rapidly than the blood compartment. Storage capacity was shown to be stratum corneum < epidermis < blood. Varying the model parameters in Table 2-4 revealed that the total amount of the chemical entering the body was sensitive to changes in epidermal blood flow. Increasing epidermal thickness and stratum corneum fat decreased the total absorbed, but increasing blood fat had no effect. Overall, the model predicts that thicker, fattier skin will provide some protection from dermal absorption of chemicals, while an increase in epidermal blood flow would increase absorption.

Validation of the model. In order to validate the model, the predicted results were compared to the experimental results of Dutkiewicz and Tyras (1967, 1968) in which male volunteers immersed their hands into a solution of 151 mg/L ethylbenzene for 1 hour. The model predicted 94% of the actual absorbed ethylbenzene dose in the human volunteers. Statistical analysis (e.g., 95% confidence limits or standard deviations of the mean) of the experimental results for the participants in the Dutkiewicz and Tyras (1967, 1968) studies were not reported by the authors and may have some impact on the accuracy of the model predictions.

Target tissues. No specific target tissues were considered in this model.

Species extrapolation. Since human data were used for validation, no species extrapolation was conducted.

Interroute extrapolation. The authors compared the inhalation, oral, and dermal dose of ethylbenzene in adults and infants that could be predicted from exposure to contaminated water in the household environment. For ethylbenzene, the dermal dose in the adult is somewhat greater than the oral or inhalation dose, based on scenarios of bathing, washing dishes, etc. In addition, the model predicts that the dermal dose (mg/kg body weight) absorbed by an infant through bathing would be greater than the adult dermal dose after whole body exposure to the same contaminated water. The authors note that since the wholebody exposures were modeled using parameters for absorption of ethylbenzene through the skin of the forearm, the predictions may be overestimations, and may require some correction.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Aromatic hydrocarbons such as ethylbenzene may only be available for intracellular metabolism and interaction if they are dissolved in aqueous solution (Sikkema et al. 1995). The movement of the chemical into the cell is thought to proceed passively from the aqueous phase, through partitioning of the compound into the lipid bilayer of the cell membrane. As a result, changes in the structure and integrity of the cell membrane may occur (see Section 2.4.2, Mechanisms of Toxicity). This, in turn, may affect membranebound enzyme activity. Evidence for this comes from the work of Engelke et al. (1993), which showed that accumulation of ethylbenzene in the microsomal membranes from pig liver altered the reduction kinetics of cytochromes P-450 and b_5. There is no evidence that the pharmacokinetic mechanisms differ in children compared to adults.

2.4.2 Mechanisms of Toxicity

Ethylbenzene has been shown to exert adverse central nervous system effects on both humans (Yant et al. 1930) and animals (Biodynamics 1986; Cragg et al. 1989; Molnar et al. 1986; Tegeris and Balster 1994; Yant et al. 1930). Although there is no specific data, there is nothing to suggest that the mechanism of toxicity is different in children compared to adults. *In vivo* animal studies of ethylbenzene toxicity at the cellular level indicate that changes in brain levels of dopamine and other biochemical alterations, and in evoked electrical activity in the brain may be involved in ethylbenzene central nervous system toxicity (Andersson et al. 1981; Frantik et al. 1994; Mutti et al. 1988; Romanelli et al. 1986).

In vitro studies of the mechanism of toxicity have focused on the effect of ethylbenzene on cell membranes, particularly that of the astrocyte (Engelke et al. 1993; Naskali et al. 1993, 1994; Sikkema et al. 1995; Vaalavirta and Tahti 1995a, 1995b). In a review by Sikkema et al. (1995), changes in the structure and integrity of the cell membrane after partitioning of ethylbenzene into the lipid bilayer may be a mechanism of toxicity. Changes in the integrity of the cell membrane may subsequently affect the function of membrane, particularly as a barrier and in energy transduction, and in the formation of a matrix for proteins and enzymes. Engelke et al. (1993) showed that incubation of pig liver microsomes with ethylbenzene caused an accumulation of ethylbenzene in the rnicrosomal membrane, which in turn increased the fluidity of the membrane. Although incubation of the microsomal membranes with ethylbenzene did not

change the content of cytochrome P-450 or cytochrome b, content, or the activities of NADPH-cytochrome P-450 reductase or NADH-cytochrome b_5 reductase, a change in the reduction kinetics of these enzymes was observed. The authors proposed that the observed change in kinetics may be due to a rearrangement of the cytochrome P-450 molecules in the microsomal membrane as a result of the accumulation of ethylbenzene in the membrane.

The work of Vaalavirta and Tahti (1995a, 1995b) and Naskali et al. (1993, 1994) has investigated the effect of ethylbenzene on the membrane of the rat astrocyte, as an *in vitro* model for the membranemediated effects of solvents on the central nervous system. Cultured astrocytes from the cerebella of neonatal Sprague-Dawley rats were sensitive to the effects of ethylbenzene, as measured by the inhibition of activity of Na+, K+-ATPase, and Mg++-ATPase (Vaalavirta and Tahti 1995a, 1995b). This effect was found to be dose-dependent (Naskali et al. 1994). Inhibition of these membrane-bound enzymes that regulate the ion channels of the membrane may disturb the ability of the cells to maintain homeostasis. Experiments with rat synaptosome preparations, similar to those using microsomal preparations by EngeIke et al. (1993), showed that membrane fluidity was increased after exposure to ethylbenzene. ATPase and acetylcholinesterase activity were also decreased, as seen in the astrocyte preparations.

2.4.3 Animal-to-Human Extrapolations

Species differences have been shown for ethylbenzene metabolism. In humans exposed via inhalation, the major metabolites of ethylbenzene are mandelic acid (approximately 70%) and phenylglyoxylic acid, which are excreted in the urine (approximately 25%) (Bardodej and Bardodejova 1970; Engstrom et al. 1984). Evidence indicates that the initial step in this metabolic pathway is oxidation of the side chain of ethylbenzene to produce 1-phenylethanol. In rats exposed by inhalation or orally to ethylbenzene, the major metabolites were identified as hippuric and benzoic acids (approximately 38%), 1-phenylethanol (approximately 25%), and mandelic acid (approximately 15-23%), with phenylglyoxylic acid making up only 10% of the metabolites (Climie et al. 1983; Engstrom 1984; Engstrom et al. 1985). In rabbits, the most important metabolite is hippuric acid, which is probably formed by oxidative decarboxylation of phenylglyoxylic acid (El Masri et al. 1958). Rabbits have been shown to excrete higher levels of glucuonidated metabolites than do humans or rats (El Masri et al. 1956; Smith et al. 1954a, 1954b). Thus, there are no animal models of ethylbenzene metabolism that are completely consistent with human metabolism. However, of the experimental models investigated, rats appear to be a more appropriate model than rabbits.

Models of the pharmacokinetic mechanisms and mechanisms of toxicity of ethylbenzene have focused on cellular processes (see Sections 2.4.1 and 2.4.2, above). In these, humans and animals appear to be similar. Although some species differences exist with respect to toxicity, adverse effects observed after ethylbenzene exposure in both humans and animals seem to be similar in scope (i.e., respiratory, hepatic, renal, and neurological). Rats may be more sensitive than mice or rabbits (Cragg et al. 1989; NTP 1992). Thus, the rat may be the most appropriate animal model for studying the mechanism of toxicity of ethylbenzene as it relates to human health effects assessment.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

Evidence from the reviewed literature has shown that ethylbenzene produces many adverse effects to both humans and laboratory animals. Clinical observations in humans and observations in animals indicate that the primary symptoms resulting from acute-duration exposure to ethylbenzene are manifested as neurological and respiratory depression and eye and throat irritation. Several studies suggest that target organs of ethylbenzene toxicity, identified in animals but not in humans, may be the liver, kidney, and hematopoietic system. These results, however, are inconclusive (particularly regarding dose-response data) given the weaknesses present in many of these studies.

Ethylbenzene is widely distributed in the environment. The exposure route of most concern to the general public is low-level inhalation exposure over long periods of time. This is due to the direct release of ethylbenzene into the air by the burning of fossil fuels or industrial processes, and partitioning into the air from other media (e.g., soil, surface water). This partitioning of ethylbenzene into the air or water would play a role in exposure to populations living near hazardous waste sites. However, in all likelihood, the most significant exposure from ethylbenzene at an uncontrolled hazardous waste site would be due to soil contact due to ethylbenzene's affinity for soil organic matter. In addition to inhalation exposure, ingestion of ethylbenzene may also be a cause of concern because trace amounts have been found in many open water supplies. This concern would be greater for those populations living near hazardous waste sites or gasoline spill sites in which water supplies have been contaminated. Issues relevant to children are explicitly discussed in Sections 2.6, Children's Susceptibility, and 5.6, Exposures of Children.

Minimal Risk Levels for Ethylbenzene.

Inhalation MRLs.

No acute-duration inhalation MRL has been derived for ethylbenzene due to a lack of appropriate data. With regard to human data, Cometto-Muniz and Cain (1995) measured eye irritation and odor thresholds for ethylbenzene. Testing sessions were for 1-2 hours starting with the highest concentration of the chemical being tested. The concentration of the compound in the headspace of each bottle was measured by gas chromatography. Eye irritation thresholds were well above odor thresholds, and eye irritation was observed at 10,000 ppm, whereas odor threshold was at 9 ppm. An eye irritation threshold/odor threshold ratio of 1,333 ppm was reported for ethylbenzene. However, this study did not describe effects that would have an adverse impact on human health, thus making it inappropriate for use in deriving an MRL.

Yant et al. (1930) observed up to six volunteers who were exposed by inhalation to 0.1, 0.2, or 0.5% (1,000, 2,000, or 5,000 ppm) ethylbenzene. At the lowest level, the volunteers reported eye irritation and burning and profuse lacrimation which gradually decreased with continued exposure. Upon entering a chamber with an ethylbenzene concentration of 2,000 ppm, the volunteers experienced severe eye irritation, throat irritation, and chest constriction. One volunteer exposed for 5 minutes to 2,000 ppm experienced vertigo. Four volunteers exposed to 2,000 ppm for 6 minutes experienced dizziness upon leaving the chamber. Three volunteers exposed to 5,000 ppm reported extreme irritation of the eyes, nose, and throat. Although this study described adverse effects of acute-duration inhalation exposure to ethylbenzene in humans, the limitations of the study include use of a few subjects per dose group, lack of data on chemical purity, and lack of control data and other study details, making the study inappropriate for use in deriving an MRL.

Other studies of acute-duration human inhalation exposure to ethylbenzene involved mixtures of solvents (Koren and Devlin 1992), evaluated genotoxic responses (Holz et al. 1995), or used ethylbenzene as a challenge agent to determine respiratory response after exposure to another chemical (Moscato et al. 1987).

- An MRL of 1 .0 ppm has been derived for intermediate-duration inhalation exposure (15-364 days) to ethylbenzene.

The intermediate-duration inhalation MRL of 1 .0 ppm was derived from a NOAEL value of 97 ppm for developmental effects in Wistar rats following inhalation exposure (Andrew et al. 1981). The ratio of the

blood/gas partition coefficients was assumed to be 1. The resulting adjusted NOAEL, 97 ppm, is equal to the human equivalent concentration (HEC) because the ratio of the blood/gas partition coefficients was assumed to be 1. The resulting $NOAEL_{(HEC)}$ 97 ppm, was then divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans after adjusting for the human equivalent concentration, and 10 for human variability) to yield the MRL value of 1 .0 ppm (see Appendix A). No adjustment for intermittent exposure was made because the pharmacokinetics of ethylbenzene indicate that the effects are most likely concentration-dependent and not duration-dependent. The choice of the NOAEL of approximately 100 ppm observed in Andrew et al. (1981) is supported by other studies. In Fischer 344/N rats, administration of 99.4 ppm ethylbenzene for 13 weeks produced no effect on absolute and relative lung or liver weight; administration of 246 ppm for the same duration caused significant increases in these parameters (NTP 1992). In a companion study, rabbits exposed to ethylbenzene using the same paradigm showed no effect on relative liver weight at 99 ppm, but increased absolute and relative liver weight at 962 ppm (Andrew et al. 1981). Although deficient in experimental details, studies reported by Ungvary and Tatrai (1985) support a NOAEL of approximately 100 ppm. In rats, exposure during gestation to ethylbenzene for 24 hours/day for 9 days at doses ranging from 138 to 552 ppm resulted in fetal resorption and retardation of skeletal development in surviving fetuses (Ungvary and Tatrai 1985). Increased incidence of extra ribs and anomalies of the urinary tract were observed at the 552 ppm dose level. No effects were observed after exposure to 138 ppm for 6 hours/day for 9 days (Ungvary and Tatrai 1985). Mice exposed to 115 ppm ethylbenzene during gestation demonstrated an increased incidence of anomalies of the urinary tract (Ungvary and Tatrai 1985). The nature of the renal malformation was not characterized and no maternal toxicity was reported. In addition, reduction in the weight of female fetuses was reported in rabbits exposed to 115 ppm during gestation (Ungvary and Tatrai 1985). Cragg et al. (1989) observed sporadic salivation in Fischer 344 rats exposed to 382 ppm ethylbenzene for 4 weeks.

No chronic-duration inhalation MRL was derived for ethylbenzene due to a lack of appropriate studies. Bardodej and Cirek (1988) monitored 200 male ethylbenzene production workers for 20 years to determine possible hazards to human health. Hematologic tests showed no detectable deviation from normal physiological limits in the parameters tested. No liver lesions or significant difference in liver function tests were reported between exposed and nonexposed humans. The authors reported that ethylbenzene concentrations in “open-type” production plants fall far below the Czechoslovakian MAC limits of 200 mg/m^3 and 1,000 mg/m^3 for average whole-shift and peak-shift concentrations but failed to report more specific concentrations. According to the authors, no incidences of cancer were reported for the last 10 years in this industrial facility in which workers were exposed to ethylbenzene. Due to the lack of quantitative exposure data, this study was not appropriate for use in the derivation of an MRL.

Angerer and Wulf (1985) and Etkina and Etkina (1995) evaluated long-term health effects of inhalation exposure of humans to mixtures of chemicals, including ethylbenzene. The confounding effects of exposure to more than one chemical make these studies inappropriate for use in deriving a chronic-duration inhalation MRL.

The NTP-sponsored 2-year toxicology and carcinogenesis studies of ethylbenzene in Fischer 344/N rats and B6C3F$_1$ mice provide the only animal data for ethylbenzene after chronic-duration exposure. Male and female rats and mice exposed to 0, 75, 250, or 750 ppm ethylbenzene by inhalation for 5 days a week, 6 hours a day for 104 weeks showed adverse health effects. Male rats exposed to 250 and 750 ppm showed body weights lower (<10%) than controls from week 20. Mean body weights of female rats were generally lower (<10%) than controls groups from week 20 and during the second year of the study. Pathological findings in male rats exposed to 750 ppm ethylbenzene showed incidences of renal tubule adenoma and adenoma or carcinoma (combined) significantly greater than incidences in the control group. An extended evaluation of the kidneys showed significant increases in incidences of renal tubule adenoma and renal tubule hyperplasia in both male and female rats exposed to 759 ppm ethylbenzene. In males exposed to 750 ppm, the incidence of renal tubule adenoma or carcinoma (combined) was significantly increased. The severity of nephropathy was increased in both male and female rats exposed to 750 ppm ethylbenzene. The incidence of interstitial cell adenoma in males exposed to 750 ppm was significantly greater than in control group and slightly exceeded the historical control range for inhalation studies. The incidence of bilateral testicular adenoma was also significantly increased in males exposed to 750 ppm. Adenoma in the testes was observed in 36 of 50, 33 of 50,40 of 50, and 44 of 50 male rats exposed to 0, 75, 250, and 750 ppm, respectively. Mean body weights of female mice exposed to 75 ppm were greater (< 10%) than those of controls from week 72 until the end of the study. No clinical findings attributed to ethylbenzene exposure was reported. The incidences of alveolar/bronchiolar adenoma and alveolar/ bronchiolar adenoma or carcinoma (combined) were significantly greater in males exposed to 750 ppm than in the controls but were within the NTP historical control range. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly greater in female mice exposed to 750 ppm than in the control group but were within the historical control ranges. In male mice, there was a spectrum of non-neoplastic changes in the liver related to ethylbenzene exposure, including syncytial alteration of hepatocytes, hepatocellular hypertrophy, and hepatocyte necrosis. In 750 ppm female mice, the incidence of eosinophilic focus was significantly increased compared to that of the control group. In female mice exposed to 250 and 750 ppm ethylbenzene, the incidences of hyperplasia of the pituitary gland pars distalis were significantly greater than those in the control group. The incidences of thyroid gland follicular cell hyperplasia were significantly greater in both males and females exposed to 750 ppm compared to controls. Although this study is well defined, it is not appropriate for use in deriving an MRL

because the NOAEL for significant non-neoplastic effects (hepatic and renal) is 250 ppm, which is greater than the NOAEL for intermediate-duration exposure.

Oral MRLs.

No acute-, intermediate-, or chronic-duration oral MRLs were derived for ethylbenzene due to a lack of appropriate data.

No studies describing acute-duration oral exposure of humans to ethylbenzene were found in the literature. Ungvary (1986) evaluated the effect of oral exposure to ethylbenzene on the estrous cycle of rats. In the fifth cycle following four normal cycles, oral doses of 500 and 1,000 mg/kg ethylbenzene were given to CFY rats in the morning of estrus, two dies&uses and proestrus. At 3:00, 4:30, and 6:00 p.m. on the day of expected proestrus, the animals were bled. Estradiol, progesterone, and luteinizing hormone levels were determined. Vaginal smears were checked daily. The uterus, ovary, and liver were examined histologically. Oral administration of 500 and 1,000 mg/kg ethylbenzene to female rats in the morning of estrus, two diestruses and proestrus decreased the peripheral hormone levels and blocked the estrous cycle during diestrus. The study limitations include lack of study details, including number of animals, and statistical analysis of data. Another study (Fouchecourt and Riviere 1996) looked at the effect of acuteduration oral exposure of animals to mixtures containing ethylbenzene.

No studies describing intermediate-duration oral exposure of humans to ethylbenzene were found in the literature. Wolf et al. (1956) evaluated the toxicity of certain alkylated benzenes and benzene, and the hazards associated with their use. Groups of 10 female rats were exposed via stomach tube to 0, 13.6, 136,408, or 680 mg/kg ethylbenzene in olive oil 5 times a week for 6 months. A group of 20 rats served as controls and were fed doses of 2.3 mL olive oil emulsified in acacia solution and kept on the same schedule as the treated rats. Hematological examinations determined on selected animals of each group after 20, 40, 80, and 130 doses included total erythrocytes and leukocytes, hemoglobin content as well as a differential blood cell count. Histopathological changes included cloudy swelling of parenchymal cells of the liver and of the kidney tubular epithelium. There were slight effects in the liver and kidney weights (no detail provided). No data were shown on the hematological examination of animals. Study limitations include use of only one sex, and failure to report purity of ethylbenzene. In addition, the study parameters were not well defined. No statistical analyses of the results were performed. Other studies (Fouchecourt and Riviere 1996; Hong et al. 1991) looked at the effect of intermediate-duration oral exposure of animals to mixtures containing ethylbenzene.

No studies describing the health effects of chronic-duration oral exposure of humans to ethylbenzene were found in the literature. The one chronic-duration oral study in animals that was found in the literature described cancer data in Sprague-Dawley rats (Maltoni et al. 1985). MRLs are not derived from cancer data.

Death. No deaths have been reported in humans following ethylbenzene exposure alone, but death has occurred in laboratory animals following acute- or chronic-duration exposure to high levels of ethylbenzene administered via the inhalation, oral, and dermal routes (Biodynamics 1986; Cragg et al. 1989; Ivanov 1962; NTP 1996; Smyth et al. 1962; Wolf et al. 1956). The concentrations of ethylbenzene necessary to cause death in animals have been shown to be relatively high (1,200-13,367 ppm, inhalation exposure; 3,500-4,728 mg/kg/day, oral exposure; 15,433 mg/kg/body weight, dermal exposure). Given this information, death in humans resulting from chronic, low-level exposure to ethylbenzene is unlikely.

Systemic Effects.

Respiratory Effects. Moderate upper respiratory irritation accompanied by chest constriction has been reported in humans exposed by inhalation to high doses (2,000 ppm) of ethylbenzene (Yant et al. 1930), but not to lower doses (Moscato et al. 1987). Animal studies support these findings and show more severe effects with increased doses (De Ceaurriz et al. 1981; Nielsen and Alarie 1982; Yant et al. 1930). The available data on adverse respiratory effects associated with ethylbenzene exposure in animals, coupled with the limited data available on humans, suggest that severe respiratory effects in humans could result following inhalation exposure to high doses of ethylbenzene. Respiratory effects from low-level exposure, such as that found in the air, would be less likely.

Cardiovascular Effects. No cardiac effects have been reported in humans exposed to ethylbenzene alone. In Russian preschool children, exposure to mixed air pollution (including ethylbenzene) was associated with increased incidence of defects of the cardiovascular system (Etkina and Etkina 1995). Studies in animals show no adverse histopathological effects after intermediate-duration inhalation exposure to concentrations up to 2,200 ppm (Cragg et al. 1989; NTP 1992; Wolf et al. 1956) or after chronic-duration inhalation exposure to concentrations up to 750 ppm (NTP 1996). Based on the data available, adverse cardiovascular effects from low-level chronic-duration exposure to ethylbenzene in the air, drinking water, or soil would be unlikely.

Gustrointestinul Effects. No studies were found describing gastrointestinal effects in humans after exposure to ethylbenzene alone. Etkina and Etkina (1995) examined the health of preschool children exposed to chemical mixtures in Russia. The main air pollutants included dust, carbon monoxide, nitric oxides, sulfur oxides, hydrogen sulfide, ammonia, hydrogen chlorous (probably HC1), sulfates, formaldehyde, benzene, toluene, xylene, ethylbenzene, phenol, benzyn (probably volatile hydrocarbons), and hydrocarbon chloride (probably chlorinated hydrocarbons). Exposure to air pollution was associated with increased incidence of defects of the digestive systems. In animals, no adverse histopathological effects were noted in the gastrointestinal system after inhalation exposure to concentrations of ethylbenzene up to 1,610 ppm (Cragg et al. 1989; NTP 1992). However, chronic-duration inhalation exposure of rats and mice to 750 ppm had no adverse effect (NTP 1996).

Hematological Effects. Studies using several species of laboratory animals exposed to ethylbenzene indicate that of the species tested, only rats are susceptible to ethylbenzene-induced hematological effects following inhalation exposure (i.e., increased platelet counts and total leukocyte counts) (Cragg et al. 1989). Other studies indicate no adverse hematological effects after inhalation exposure at equivalent or higher doses (NTP 1992; Wolf et al. 1956). Because of these observed interspecies differences following inhalation exposure and a lack of data following oral and dermal exposures, it is unknown whether hematological effects might occur in humans following exposure to ethylbenzene.

Musculoskeletul Effects. No musculoskeletal effects in humans have been reported in the available literature. Inhalation studies in animals have indicated that exposure to ethylbenzene results in impaired motor coordination, but this may be due more to central nervous system effects that musculoskeletal effects (Tegeris and Balster 1994). Histopathological examination of bone tissue in animals after intermediateduration inhalation exposure to concentrations up to 1,610 ppm showed no adverse effects (Cragg et al. 1989; NTP 1992). Therefore, based on the limited data available, it seems unlikely that musculoskeletal effects would be of concern after low-level chronic-duration exposure to ethylbenzene.

Hepatic Effects. No hepatotoxic effects in humans have been reported in the available literature. Inhalation studies in animals suggest that biochemical changes, changes in liver weight, and histopathological alterations in the liver may be related to dose and duration of exposure to ethylbenzene (Biodynamics 1986; Cragg et al. 1989; Elovaara et al. 1985; NTP 1992, 1996; Toftgard and Nilsen 1982 Wolf et al. 1956). These biochemical changes are accompanied by hepatic hypertrophy, with increased microsomal enzyme activity (Elovaara et al. 1985; Fouchecourt and Riviere 1996). These results are

supported by an intraperitoneal study in rats that demonstrated marked increases in liver enzyme activity (Pyykko et al. 1987). Similar hepatic alterations in mice and rats exposed orally and by inhalation suggest that these effects might occur in humans, but no definitive conclusions can be drawn given the weaknesses of some of the studies, as outlined earlier (Biodynamics 1986; Cragg et al. 1989; Elovaara et al. 1985; Toftgard and Nilsen 1982; Wolf et al. 1956). Despite these weaknesses, the data suggest that humans exposed to ethylbenzene in high concentrations, particularly individuals with compromised liver function, may be at increased risk for ethylbenzene-induced hepatic effects.

Renal Effects. Renal effects, manifested as enzyme changes, increases in organ weight, and tubular swelling or hyperplasia, have been observed in rats and mice (Andrew et al. 1981; Biodynamics 1986; Cragg et al. 1989; NTP 1992, 1996; Toftgard and Nilsen 1982; Wolf et al. 1956). These studies suggest that renal effects may occur in humans exposed to high doses of ethylbenzene. However, significant weaknesses exist in several of these studies. Despite these weaknesses, the data suggest that humans exposed to ethylbenzene in high concentrations, particularly individuals with compromised kidney function, may be at increased risk for ethylbenzene-induced renal effects.

Endocrine Effects. In Russian preschool children, exposure to mixed air pollution (including ethylbenzene) was associated with endocrine effects (Etkina and Etkina 1995). Hormonal imbalance was observed in often ill children which was manifested in increased concentrations of thyrotropin (thyroid-stimulating hormone or TSH), adrenocorticotrophic hormone (ACTH), growth hormone (GH), cortical, and T4. Frequent illnesses did not influence plasma concentration of T3. Children exposed to moderate pollution were observed to have increased activity of endocrine agents, having pronounced diabetogenic effect and catabolic direction of metabolic processes. Children exposed to intense air pollution showed decreased GH, ACTH, T4, cortisol, TSH, and T3. The analysis of interhormonal coefficients showed that exotoxicants disturb interrelations between the central and peripheral endocrine organs, distort interhypophyseal and intrathyroid connections. Studies in animals indicate no adverse histopathological changes to the tissues of endocrine organs after acute- or intermediate-duration inhalation exposure to concentrations up to 2,200 ppm (Cragg et al. 1989; NTP 1992; Wolf et al. 1956). Tissues examined included adrenal, pancreas, pituitary, thyroid, and parathyroid glands. However, mice (but not rats) exposed to 750 ppm ethylbenzene for 2 years exhibited hyperplastic changes in the thyroid gland (NTP 1996). No evaluations of the effect of ethylbenzene on endocrine function were found in the literature. However, based on the limited data available, it seems unlikely that exposure to ethylbenzene at levels found in the environment would cause adverse effects on the endocrine system of the exposed population.

Ocular Effects. Ethylbenzene vapors have been shown to cause ocular irritation, burning, and lacrimation in exposed individuals (Cometto-Muniz and Cain 1995; Thienes and Haley 1972; Yant et al. 1930). Animal studies show similar effects (Biodynamics 1986; Cragg et al. 1989; Tegeris and Balster 1994; Yant et al. 1930). These effects occurred at relatively high concentrations. Thus, ocular irritation would be of concern to populations exposed to high concentrations of ethylbenzene in the air, such as in the occupational setting, but would not likely be of concern at exposure levels found in the environment.

Body Weight Effects. No effects on body weight have been reported in humans after exposure to ethylbenzene alone. In Russian preschool children, exposure to mixed air pollution (including ethylbenzene) was associated with inhibited physical development marked by lower weights (no data shown) in seldom ill children (Etkina and Etkina 1995). In animals, body weight was not a reliable indicator of ethylbenzene toxicity, even at relatively high exposure concentrations (Andrew et al. 1981; Biodynamics 1986; Cragg et al. 1989; NTP 1992, 1996; Romanelli et al. 1986; Wolf et al. 1956). Thus, it is unlikely that changes in body weight would occur in populations chronically exposed to low levels of ethylbenzene such as those found in the environment.

Metabolic Effects. Metabolic effects reported after exposure to ethylbenzene are limited to induction of liver and kidney enzymes in animals (Elovaara et al. 1985; Toftgard and Nilsen 1982). The data suggest that humans exposed to ethylbenzene in high concentrations, particularly individuals with compromised liver or kidney function, may be at increased risk for ethylbenzene-induced effects on enzyme activity.

Other Systemic Effects. Food consumption has been monitored in animal experiments after ethylbenzene exposure and does not appear to be a sensitive indicator of toxicity (Andrew et al. 1981). No other suitable measures of toxicity were found in the literature.

Immunological and Lymphoreticular Effects. No studies were found that described immunological and lymphoreticular effects of exposure of humans to ethylbenzene alone. In Russian preschool children, exposure to mixed air pollution (including ethylbenzene) was associated with increased allergic diseases (Etkina and Etkina 1995). A dose-dependent inhibition of functional activity of the cellular immunity was mostly manifested in often ill children even at low levels of air pollution. IgM was observed to increase in high levels of pollution. At increased levels of pollution, the children revealed an apparent tendency towards reduction of phagocytic index and an increase in the number of phagocytic neutrophils. Data describing effects of ethylbenzene exposure are limited to animal studies (Andrew et al.

1981; Cragg et al. 1989; NTP 1992, 1996; Wolf et al. 1956). These studies looked at gross appearance; organ weight; and histopathology of the spleen, lymph nodes, bone marrow, and thymus, and reported no adverse effects. No evaluations of immunological function were conducted. However, it seems unlikely that immunological effects would be of concern to populations chronically exposed to low levels of ethylbenzene found in the environment.

Neurological Effects. The principal effect in humans acutely exposed via inhalation to high concentrations of ethylbenzene has been central nervous system toxicity (dizziness, vertigo) (Yant et al. 1930). Complete recovery has been shown to occur following acute exposure. Central nervous system effects have also been observed in animal studies (Biodynamics 1986; Cragg et al. 1989; Molnar et al. 1986; Tegeris and Balster 1994; Yant et al. 1930). Changes in evoked electrical activity in the brain have been observed (Frantik et al. 1994). Biochemical alterations were observed in animal studies in which dopamine depletion in the brain following exposure to high concentrations of ethylbenzene was reported. It was suggested that changes in the dopamine levels and turnover might disturb catecholamine neurotransmission in the brain leading to altered brain function (Andersson et al. 1981; Mutti et al. 1988). However, data are available that show increased dopamine turnover, but brain tissue levels remaining constant in all but one of the regions of the brain examined (Andersson et al. 1981). Recent *in vitro* studies indicate that ethylbenzene exposure alters the metabolic activity of astrocytes and synaptosomes (Naskali et al. 1993, 1994; Vaalavirta and Tahti 1995a, 1995b). Given the available human and supporting animal data, there is considerable likelihood that human populations acutely exposed to high concentrations of ethylbenzene are at risk for developing neurological effects. The neurological effects of long-term exposure of humans to ethylbenzene are unknown.

Reproductive Effects. No studies on the reproductive effects in humans following exposure to ethylbenzene were found. Oral administration of ethylbenzene resulted in blockage of the estrus cycle in female rats (Ungvary 1986). This study had many weaknesses (e.g., small number of test animals, no statistical analysis) that prevent definitive conclusions from being drawn. Decreased fertility in female rats was reported following inhalation exposure to ethylbenzene but was not considered to be significant by the authors (Andrew et al. 1981). In addition, increased postimplantation death was reported in rats, and abortions were observed in rabbits, but no effects were seen in mice (Ungvary and Tatrai 1985). The data are insufficient to eliminate the possibility of female reproductive effects. Data describing histopathological evaluation of male reproductive tissues are primarily negative (Biodynamics 1986; Cragg et al. 1989; NTP 1992). Wolf et al. (1956) reported degeneration of the germinal epithelium in one monkey and

one rabbit, but the study had many weaknesses (no numerical data or statistical analysis, insufficient experimental details). Thus, based on the limited data in animals, no conclusion can be drawn concerning the effect of ethylbenzene on reproductive competence in humans. However, the NTP-sponsored 2-year bioassay revealed a significant increase in interstitial cell adenoma and bilateral testicular adenoma in rats, but not mice at 750 ppm ethylbenzene. Thus, male reproductive tissues may be a target for ethylbenzene toxicity.

Developmental Effects. No reports of developmental toxicity following exposure to ethylbenzene in humans were located. The available information from animal studies indicates that inhalation exposure of pregnant rats to ethylbenzene can produce minimal fetotoxic effects at doses that may or may not induce minimal maternal changes (i.e., increased relative liver, kidney, and spleen weights) (Andrew et al. 1981; Ungvary and Tatrai 1985). Mice exposed to 115 ppm ethylbenzene during gestation demonstrated an increased incidence of anomalies of the urinary tract (Ungvary and Tatrai 1985). The nature of the renal malformation was not characterized, and no maternal toxicity was reported. This report contained very few experimental details. Andrew et al. (1981) however, provides a well-defined study in which developmental changes were observed. These developmental effects consisted of an increase in the incidence of supernumerary ribs, which is a non-specific indicator of variation in the development of the skeletal system of rodents. No developmental effects were seen in rabbits exposed to similar levels of ethylbenzene (Andrew et al. 1981). Because of observed interspecies differences, the relevance of these findings with regard to developmental effects in humans cannot be ascertained.

Genotoxic Effects. Holz et al. (1995) reported no increase in sister chromatid exchanges, DNA adduct formation, micronuclei, or DNA single-strand breaks in the peripheral lymphocytes of workers exposed to low levels of ethylbenzene in a styrene plant. NTP (1996) showed no increase in micronucleated peripheral erythrocytes in mice exposed to 750 ppm ethylbenzene for 13 weeks. Another *in vivo* study investigated the genotoxic effects of ethylbenzene and reported no dose-dependent increase in the frequency of micronucleated polychromatic erythrocytes (Mohtashamipur et al. 1985). This study is limited by inadequate sampling time. In addition, the type of clastogenic effect occurring cannot be defined. These data are shown in Table 2-5.

However, the genotoxic potential of ethylbenzene has been investigated primarily using *in vitro* assays in *Salmonella typhimurium* (Dean et al. 1985; Florin et al. 1980; Nestmann et al. 1980; NTP 1986, 1996), *Escherichia coli* (Dean et al. 1985), *Saccharomyces cerevisiae* (Dean et al. 1985; Nestmann and Lee

Table 2-5. Genotoxicity of Ethylbenzene *In Vivo*

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Mammalian cells:				
Mouse (peripheral erythrocytes)	Micronuclei	NA	–	NTP 1996
Human (occupational exposure/ peripheral lymphocytes)	DNA adducts, micronuclei, sister chromatid exchange, DNA strand breaks	NA	–	Holz et al. 1995

NA = not applicable; – = negative results

1983), Chinese hamster ovary cells (NTP 1986, 1996), mouse lymphoma cells (McGregor et al. 1988; NTP 1996), and human lymphocytes (Norppa and Vainio 1983a). Results of these in vitro genotoxicity studies are shown in Table 2-6. The available data indicate that ethylbenzene is not mutagenic in bacteria or yeast cells in the presence or absence of metabolic activation. Ethylbenzene also failed to induce sister-chromatid exchanges and chromosomal aberrations in Chinese hamster cells. A weak positive response was observed when ethylbenzene was tested for sister chromatid exchanges in human lymphocytes (Norppa and Vainio 1983a).

Mutagenicity of ethylbenzene was studied in *S. typhimurium* strains TA97, TA98, TA100, TA1535, TA1537, and TA1538 (Dean et al. 1985; Florin et al. 1980; Nestmann et al. 1980; NTP 1986, 1996) and *E. coli* strains WP_2 and WP_2uvrA (Dean et al. 1985) both in the presence and absence of an S9 mixture. Ethylbenzene was not mutagenic in *S. typhimurium* or *E. coli.*

In gene conversion assays conducted in *S. cerevisiae* strains JDl (Dean et al. 1985), XVl85-14C, and D7 (Nestmann and Lee 1983) no increases in mutation frequencies were detected following application of ethylbenzene. Details of the dose levels tested were not provided.

The potential of ethylbenzene to induce chromosomal aberrations and sister chromatid exchanges was studied in Chinese hamster ovary cells (NTP 1986, 1996). No mutagenic response was observed at dose levels of 75, 100, or 125 mg/L in either assay. However, ethylbenzene was found to be mutagenic at 80 mg/L without metabolic activation, and lethal to cells at 100 mg/L in the mouse lymphoma assays (McGregor et al. 1988). Concentrations of ethylbenzene used ranged from 10 to 160 mg/L. No doseresponse was reported. Ethylbenzene induced a marginal, although significant ($p<0.0l$), increase in sister chromatid exchanges in human lymphocytes but only at the highest dose tested (1,061.6 mg/L), which was also toxic to the cells (Norppa and Vainio 1983a). The relevance of these findings with regard to genotoxic effects of ethylbenzene in humans is not known.

In summary, genotoxicity studies on ethylbenzene have provided negative results in a variety of *in vitro* assays using numerous prokaryotic organisms, S. *cerevisiae,* and Chinese hamster ovary cells and rat liver epithelial cells, and in an *in vivo* assay using mouse bone marrow cells. It has, however, caused a mutagenic effect in mouse lymphoma cells and has been shown to induce a marginal yet significant increase in sister chromatid exchanges in human lymphocytes. Although the majority of the data suggest that

Table 2-6. Genotoxicity of Ethylbenzene *In Vitro*

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium (plate incorporation assay)	Gene mutation	–	–	Dean et al. 1985[a]; Florin et al. 1980[b]; Nestmann et al. 1980[c]
S. tymphimurium (plate incorporation assay; strains TA87, TA98, TA100, TA1537; TA1538)	Gene mutation	–	–	NTP 1986[d]
S. tymphimurium (plate incorporation assay; strains TA97, TA98, TA100, TA1535)	Gene mutation	–	–	NTP 1996[d]
Escherichia coli WP_2, WP_2uvrA	Gene mutation	–	–	Dean et al. 1985[a]
Eukaryotic ornganisms:				
Saccharomyces cerevisiae JD1 gene conversion assay	Gene mutation	–	–	Dean et al. 1985
S. cerevisiae Dy, XV185-14C	Gene mutation	–	ND	Nestmann and Lee 1983
Mammalian cells:				
Mouse lymphoma cells	Gene mutation	ND	+	McGregor *et al. 1988*
Mouse lymphoma cells	Gene mutation	ND	+	NTP 1996
Rat liver (RL4) epithelial type cells/chromosome assay	Chromosome damage	–	–	Dean et al. 1985
Chinese hamster ovary cells	Sister chromatid exchange	–	–	NTP 1986
Chinese hamster ovary cells	Sister chromatid exchange	–	–	NTP 1996
Chinese hamster ovary cells	Chromosome damage	–	–	NTP 1996

[a]Concentrations of ethylbenzene tested: 0, 0.2, 2, 20, 500, 2,000 µg/plate (>99% pure)
[b]Concentrations of ethylbenzene tested: 0, 3, 31, 318, or 3,184 µg/plate (0, 0.03, 0.3, 3, or 30 µmole/plate)
[c]Concentrations of ethylbenzene tested: Up to 0.4 mg/plate, a concentration causing lethality
[d]Concentrations of ethylbenzene tested: 0, 10, 33, 110, 333, 666, or 1,000 µg/plate
[e]Weakly positive

ND = no data; – = negative results; + = positive results

ethylbenzene is not mutagenic in most systems, the two studies that did show positive results suggest that ethylbenzene may cause an increase potential for genotoxicity in humans.

Cancer. No association between increased cancer incidence in humans and exposure to ethylbenzene has been reported in current literature. Both chronic bioassays located in the literature showed a significant increase in tumors in rats, either exposed by inhalation (NTP 1996) or orally exposed (Maltoni et al. 1985). The NTP (1996) study provides clear evidence of carcinogenicity in male Fischer 344/N rats exposed to 750 ppm ethylbenzene for up to 2 years, citing the incidence of renal and testicular lesions. Evidence for female rats and male and female B6C3F_1 mice is suggestive, but not conclusive. The results from the Maltoni et al. (1985) study, however, are inconclusive, given the weaknesses of the study (e.g., only one dose was tested and no survival data were provided).

In the 1996 Integrated Risk Information System (IRIS 1996) database, EPA has classified ethylbenzene as a Group D agent (Not Classifiable as to Carcinogenicity). This classification applies to those chemical agents for which there is inadequate evidence of carcinogenicity in humans or animals. No potency factor (q_1*) or other quantitative estimate of carcinogenicity has been developed by EPA for ethylbenzene. The International Agency for Research on Cancer (IARC) and the National Toxicology Program (NTP) have yet not classified this chemical for carcinogenicity. However, based on the findings of the recent NTP report (NTP 1996), this is likely to change in the near future.

2.6 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate due to maternal exposure during gestation and lactation. Relevant animal and in vitro models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 5.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both pre-natal and post-natal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns and at various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults and sometimes unique enzymes may exist at particular developmental stages (Komori 1990; Leeder and Keams 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in the newborn who has a low glomerular filtration rate and has not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

There are no data describing the effect of exposure to ethylbenzene on children or immature animals. Respiratory and eye irritation, and dizziness are the most prevalent signs of exposure to high levels of

ethylbenzene (Yant et al. 1930), and it is expected that children would also exhibit these effects, as well as other effects observed in adults. Minor birth defects have occurred in newborn rats, but not rabbits, whose mothers were exposed by breathing air contaminated with ethylbenzene (Andrew et al. 1981; Ungvary and Tatrai 1985). These defects consisted of urinary tract anomalies, and supernumerary ribs, a frequently observed indicator of variation in the development of the skeletal system in rodents. Supernumerary ribs were observed in the presence of minimal maternal changes. Section 2.2.1.6, Developmental Effects, contains a more detailed discussion of these results. A significant increase in the incidence of extra ribs occurred at only one dose during gestation in the study by Andrews et al. (1981). The report by Ungvary and Tatrai (1985) lacks pertinent experimental details that would strengthen the validity of their results. In addition, it is not known whether these developmental effects would be observed in people. There are no human developmental data. Ethylbenzene has been detected in human breast milk at unspecified concentrations (Pellizzari et al. 1982), but no pharmacokinetic experiments have been done to confirm that it is actually transferred to breast milk in mammals. It is not known if ethylbenzene crosses the placenta.

Since there is no information about health effects in children, it is unknown whether they differ from adults in their susceptibility to health effects from ethylbenzene. There is no specific information about the metabolism of ethylbenzene in children or immature adults. However, since two of the enzyme families responsible for the conjugation and elimination of ethylbenzene are developmentally regulated, it is possible that the activity of these enzymes would differ in children or immature animals compared to adults. In humans, UDP glucuronosyltransferase activity does not reach adult levels until about 6-l 8 months of age, although the development of this activity is isoform specific. Activity of sulfotransferases (which is also isoform specific) seems to develop earlier. The activity of some sulfotransferase isoforms may even be greater during infancy and early childhood than in adulthood (Leeder and Keams 1997).

2.7 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC 1989b). The preferred

biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to ethylbenzene are discussed in Section 2.7.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by ethylbenzene are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.9, Populations That Are Unusually Susceptible.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Ethylbenzene

Information on ethylbenzene concentrations in human tissue or fluids is available. Exposure to ethylbenzene can be determined by the detection of mandelic acid and phenylglyoxylic acid in urine or by direct detection of ethylbenzene in whole human blood. The only available study that associated levels of ethylbenzene in human tissue and fluids with health effects was conducted by Angerer and Wulf (1985). In this study, specimens of whole blood from 35 male workers chronically exposed to organic solvents

containing ethylbenzene were analyzed. The mean ethylbenzene concentrations detected from personal air monitoring was 4 ppm, and the corresponding mean concentration of ethylbenzene in the blood samples was 61.4 μg/L. Significant correlations between the concentrations of ethylbenzene in air and blood and leukocyte counts were reported. However, blood lead levels could have been a confounding factor.

The 1982 National Human Adipose Tissue Survey conducted by EPA measured ethylbenzene in 96% of the 46 composite samples analyzed for volatile organic compounds (Stanley 1986). A wet tissue concentration range of not detected (detection limit=2 ng/g) to 280 ng/g was reported, but an average concentration was not provided.

Numerous studies indicate that environmental exposures to ethylbenzene can result in detectable levels in human tissues (Antoine et al. 1986; Cramer et al. 1988; Pellizzari et al. 1982; Wolff 1976; Wolff et al. 1977) and in expired air (Conkle et al. 1975; Engstrom and Bjurstrom 1978; Wallace et al. 1984). Analysis of blood specimens from a test population of 250 patients (Antoine et al. 1986) and composite samples obtained from blood donations of laboratory personnel with potentially low-level exposure (Cramer et al. 1988) indicated ethylbenzene concentrations in the blood to range from below detection limits to 59 ppb. Similarly, ethylbenzene was detected in 8 of 12 milk samples from lactating women living in various urban areas of the United States with high probability of emissions of pollutants (Pellizzari et al. 1982). Subcutaneous fat samples taken from individuals exposed to an average of l-3 ppm ethylbenzene in the workplace contained ethylbenzene levels as high as 0.7 ppm (Wolff 1976; Wolff et al. 1977).

Studies examining the correlation of ethylbenzene concentrations in ambient air with concentrations measured in expired or alveolar air have also been conducted (ConkIe et al. 1975; Engstrom and Bjurstrom 1978; Wallace et al. 1984). Ethylbenzene concentrations in breath samples were reported to correlate well with ethylbenzene concentrations in indoor samples taken with personal air monitors (Wallace et al. 1984). A correlation was also found between ethylbenzene uptake and ethylbenzene concentrations in alveolar air during, but not after, inhalation exposure in human volunteers (Engstrom and Bjurstrom 1978). Rates of ethylbenzene expiration measured in volunteers with no known previous exposure to ethylbenzene ranged from 0.78 μg/hour to 14 μg/hour, with higher rates detected in smokers than in nonsmokers (Conkle et al. 1975).

2.7.2 Biomarkers Used to Characterize Effects Caused by Ethylbenzene

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

No specific biornarkers of effect for ethylbenzene were identified. Most of the information on humans is from case reports in which the effects are general and non-specific, such as eye and throat irritation and chest constriction (Yant et al. 1930).

There is one study that indicates that the average number of lymphocytes increased ($p=0.005$) and hemoglobin levels decreased ($p=0.001$) following exposure of 35 men to ethylbenzene (Angerer and Wulf 1985), but these data were not substantiated in a long-term study on 200 occupationally exposed male workers (Bardodej and Cirek 1988). Given the nonspecificity of these end points and the presence of blood lead levels that could confound the results (Angerer and Wulf 1985), it would be difficult to correlate changes in these parameters with exposure to ethylbenzene.

2.8 INTERACTIONS WITH OTHER CHEMICALS

Interaction of ethylbenzene with carbon monoxide, phenobarbital, and *m*-xylene have been described in numerous studies. Carbon monoxide has been shown to inhibit the *in vitro* hydroxylation of ethylbenzene when the ratio of carbon monoxide to atmospheric oxygen is 2 to 1 (Maylin et al. 1973). Similarly, simultaneous exposure of rats to ethylbenzene and xylenes has produced inhibitory effects on ethylbenzene metabolism as evidenced by a decreased excretion rate of urinary ethylbenzene metabolites (Angerer and Lehnert 1979; Elovaara et al. 1984; Engstrom et al. 1984). Similar metabolic inhibitory effects were seen in female rats intraperitoneally pretreated with ethanol before inhalation exposure to ethylbenzene as evidenced by significantly increased ethylbenzene blood levels compared with animals pretreated with physiological saline (Romer et al. 1986). The authors suggested that increased central nervous system disturbances (e.g., depression) may be expected following simultaneous exposure to ethylbenzene and ethanol. Conversely, pretreatment with phenobarbital has been shown to increase the rate of ethylbenzene oxidation both in vitro (Maylin et al. 1973; McMahon and Sullivan 1966) and *in vivo* in rats (McMahon and Sullivan 1966).

Though no further studies were located that demonstrate specific interactions of ethylbenzene with other chemicals, a number of substances are known to influence the metabolism of many xenobiotics. For instance, the metabolism of ethylbenzene can be markedly altered by inhibitors (e.g., SKF 525A) and inducers (e.g., phenobarbital, described above) of drug-metabolizing enzymes (Gillette et al. 1974) and by the availability of detoxication agents (e.g., glucuronic acid or sulfates) that bind ethylbenzene metabolites and subsequently are excreted from the body. Mono-oxygenases (MOs) are a class of enzymes involved in the detoxication of xenobiotics, including ethylbenzene. Substances that induce MO enzymes may decrease the toxicity of ethylbenzene by increasing the rate of production of its less toxic metabolites. Conversely, MO enzyme inhibitors would be expected to have the opposite effect. Compounds that affect glucuronic acid availability could also affect the excretion rate of ethylbenzene metabolites.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to ethylbenzene than will most persons exposed to the same level of ethylbenzene in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxication or excretion of ethylbenzene, or compromised function of target organs affected by ethylbenzene. Populations who are at greater risk due to their unusually high exposure to ethylbenzene are discussed in Section 5.6, Populations With Potentially High Exposure.

Even though ethylbenzene is not known to bioaccumulate, human and animal studies suggest that several factors can contribute to an increased probability of adverse health effects following ethylbenzene exposure (Mackinson et al. 1978). Exposure of individuals with impaired pulmonary function to ethylbenzene in air has been shown to exacerbate symptoms because of ethylbenzene's irritant properties. Because ethylbenzene is detoxified primarily in the liver and excreted by the kidney, individuals with liver or kidney disease might be more susceptible to ethylbenzene toxicity, as would persons taking medications or other drugs (e.g., alcohol) that are known hepatotoxins. Persons with dermatitis or other skin diseases may be at greater risk, since ethylbenzene is a defatting agent and may aggravate these symptoms. Children's susceptibility is discussed in Section 2.6.

In summary, groups that might be more susceptible to the toxic effects of ethylbenzene are individuals with diseases of the respiratory system, liver, kidney, or skin; young children; fetuses; pregnant women; and individuals taking certain medications such as hepatotoxic medications or drugs.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to ethylbenzene. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to ethylbenzene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. No information specifically addressing treatment following exposures to ethylbenzene was found.

The following texts provide specific information about treatment following exposures to styrene, a similar compound:

Carl Zenz et al. (eds.) (1994). Occupational Medicine, 3rd edition. Mosby, St. Louis.

Ellenhorn, MJ and Barceloux, DG (eds.) (1988). Medical Toxicology: Diagnosis and Treatment of Human Poisoning. Elsevier Publishing, New York, NY.

2.10.1 Reducing Peak Absorption Following Exposure

Human exposure to ethylbenzene can occur by inhalation, oral, or dermal contact. General recommendations for reducing absorption of ethylbenzene were not found in the literature. Recommendations for reducing absorption of styrene [C_8H_8], a chemically and structurally similar compound to ethylbenzene [C_8H_{10}], are provided here.

The removal of the patient from the source of contamination is an initial priority along with proper ventilation and cardiac monitoring. Recommendations included the removal of all contaminated clothing and thorough washing of exposed areas with green soap and water. If the patient is alert, syrup of ipecac is recommended following ingestions exceeding 2-3 mL/kg. For patients at risk because of obtundation, intubation should precede lavage (Ellenhorn and Barceloux 1988; Zenz 1994). If a smaller quantity has been ingested, a physician should be called immediately. Syrup of ipecac or other means of inducing vomiting is not recommended for ingestion of smaller quantities since ethylbenzene can directly enter the

lungs if swallowed, or if subsequently vomited, due to its low viscosity (32 SUS at 100°F). Once in the lungs, it can cause chemical pneumonitis, pneumonia, and pulmonary edema (Gossel and Bricker 1994).

2.10.2 Reducing Body Burden

Following absorption into the blood, ethylbenzene is rapidly distributed throughout the body. The initial stage of ethylbenzene metabolism in humans is the formation of 1-phenylethanol via hydroxylation of the of the side chain. Further oxidation leads to the formation of mandelic acid and phenylglyoxylic acid, the major urinary metabolites of ethylbenzene in humans. Detoxication pathways generally involve the formation of glucuronide or sulfate conjugates of 1 -phenylethanol or its subsequent metabolites. Urinary excretion is the primary route of elimination of metabolized ethylbenzene. Studies in humans and animals indicate that urinary excretion occurs in several phases, with half-lives of hours. Hence, ethylbenzene and its metabolites have relatively short half-lives in the body, and while some of these metabolites are clearly toxic, substantial body burdens are not expected.

No methods are currently used for reducing the body burden of ethylbenzene. It is possible that methods could be developed to enhance the detoxication and elimination pathways.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

Aromatic hydrocarbons, such as ethylbenzene, may only be available for intracellular interaction if they are dissolved in aqueous solution (Sikkema et al. 1995). Changes in the structure and integrity of the cell membrane may occur after the chemical molecule dissolves into the lipid bilayer of the membrane. Changes in the integrity of the cell membrane may subsequently affect the function of membrane, particularly as a barrier and in energy transduction, and in the formation of a matrix for proteins and enzymes. The work of Vaalavirta and Tahti (1995a, 1995b) and Naskali et al. (1993, 1994) suggests that changes in the cell membrane caused by ethylbenzene may disturb the ability of the cell to maintain homeostasis. Experiments with rat synaptosome preparations showed that membrane fluidity was increased after exposure to ethylbenzene, accompanied by changes in the activity of membrane-bound enzymes. It is possible that stabilizing the cell membrane so that the ethylbenzene would be unable to enter the lipid bilayer could provide protection against the subsequent toxic effects of the compound.

Ethylbenzene has been shown to exert adverse central nervous system effects on both humans (Yant et al. 1930) and animals (Biodynamics 1986; Cragg et al. 1989; Molnar et al. 1986; Tegeris and Balster 1994; Yant et al. 1930). In vivo animal studies of ethylbenzene toxicity at the cellular level indicate that changes in brain levels of dopamine and other biochemical alterations, and in evoked electrical activity in the brain may be involved in ethylbenzene central nervous system toxicity (Andersson et al. 1981; Frantik et al. 1994; Mutti et al. 1988; Romanelli et al. 1986). Treatment measures aimed at preventing these changes in neurotransmitter levels and electrical activity may serve to lessen or prevent the central nervous system effect of ethylbenzene exposure.

2.11 ADEQUACY OF THE DATABASE

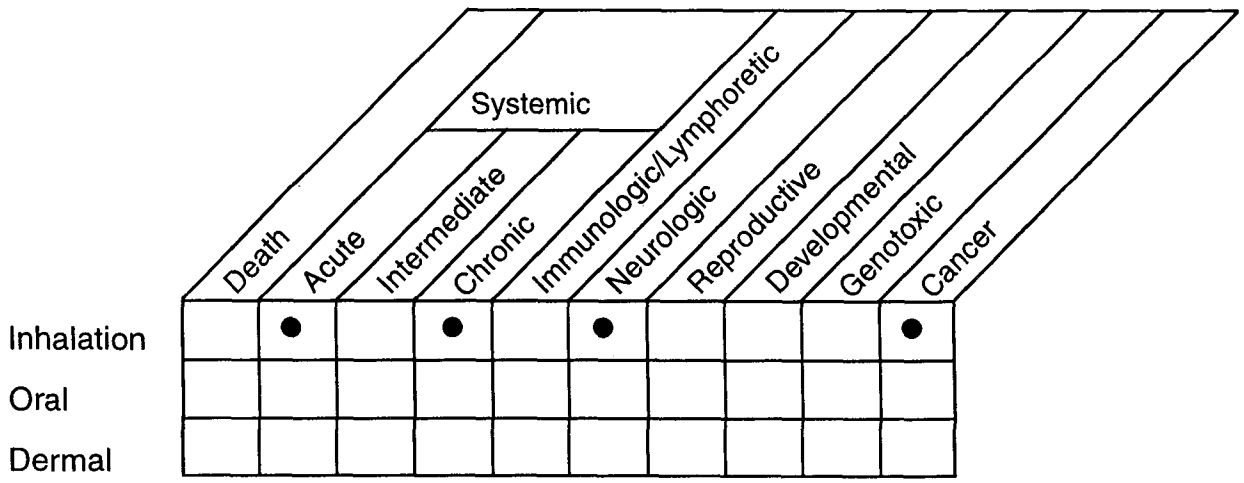
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ethylbenzene is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of ethylbenzene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

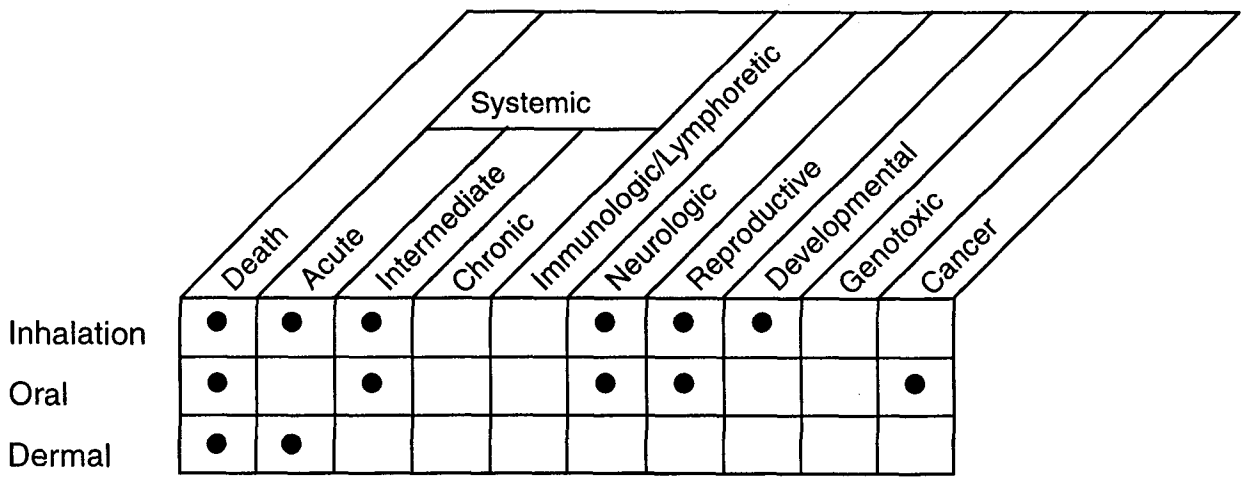
2.11.1 Existing Information on Health Effects of Ethylbenzene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to ethylbenzene are summarized in Figure 2-6. The purpose of this figure is to illustrate the existing information concerning the health effects of ethylbenzene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific

Figure 2-6. Existing Information on Health Effects of Ethylbenzene



Human



Animal

● Existing Studies

information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 2-6 graphically describes the existing health effects information on ethylbenzene by route and duration of exposure. Little information concerning humans exposed via inhalation to ethylbenzene is available. Most of the information concerning health effects in humans is reported in occupational studies, which are difficult to interpret given the limitations of the studies (e.g., simultaneous exposure to other hazardous substances, unquantified exposure concentrations, and exposure probably occurring by a combination of routes). No data were available concerning human health effects following oral or dermal exposures to ethylbenzene. Dermal effects in humans are limited to respiratory and/or ocular irritation after exposure to ethylbenzene vapor.

In animals, the lethality of ethylbenzene is documented for all routes of exposure. Systemic health effects following inhalation exposure to ethylbenzene for acute and intermediate durations as well as immunologic, neurologic, developmental, and reproductive effects are also described. Limited data on the health effects resulting from oral or dermal exposure to ethylbenzene were located. No chronic systemic or genotoxic studies were located for the oral, inhalation, or dermal routes of exposure.

2.11.2 Identification of Data Needs

In general, data on the toxic effects of ethylbenzene in humans and animals are limited. In many areas for which studies have been conducted, the lack of reliable data precludes any definitive conclusions from being drawn and the development of corresponding MRLs.

Acute-Duration Exposure. Inhalation exposure of humans to ethylbenzene results in irritation of the eyes and lungs. In addition, neurological effects such as dizziness have been reported in humans following acute-duration exposure to this chemical. Similarly, respiratory and neurological effects have been observed in animals exposed to ethylbenzene via inhalation. However, only one dose level was used in many of the studies; therefore, information on dose-response relationships was not available. Furthermore, data for acute-duration oral exposure to ethylbenzene are lacking. No acute-duration studies were suitable for deriving inhalation or oral MRLs for ethylbenzene. Well conducted acute-duration studies via inhalation and the oral route, using a number of exposure concentrations and well defined protocols would be useful in establishing this dose-response relationship and elucidating any thresholds that may exist for

acute adverse health effects. The potential for brief human exposure to high concentrations of ethylbenzene exists in accidental exposure in the workplace, hazardous waste sites, and gasoline spill sites.

Intermediate-Duration Exposure. No intermediate-duration studies were located for humans exposed to ethylbenzene by the inhalation, oral, or dermal routes. Repeated inhalation exposures of animals to ethylbenzene have been evaluated. Respiratory, hepatic, renal, and neurological effects have been characterized in animals (Andrew et al. 1981; Cragg et al. 1989; Elovaara et al. 1985; NTP 1992). No intermediate-duration studies were suitable for deriving oral MRLs for ethylbenzene. The NTP 90-day inhalation study (NTP 1992) provides additional information on systemic toxicity following inhalation exposure. Additional histopathology data resulting from repeated oral exposure would be particularly useful, since the potential exists for humans to be exposed to ethylbenzene in the drinking water. These data would help confirm that the liver and kidney are target organs and determine sensitive end points in the liver and kidney, which appear to be the target organs following intermediate-duration exposure to ethylbenzene. There are data (Fouchecourt and Riviere 1996) suggesting that the lung may be a target, but these data need to be confirmed. Presently, one study exists that may suggest the occurrence of histopathological changes in the liver and kidney following repeated oral exposure to ethylbenzene (Wolf et al. 1956). However, these results are marked by limitations in the methodology, the end points monitored, and the reporting of data; therefore, no definitive conclusions can be drawn. Data on intermediate-duration dermal exposure in humans are lacking, and in animals are limited to effects of exposure of mucous membranes to ethylbenzene vapor. Such information would also be useful in determining human health effects, since the potential exists, both in the occupational setting and at hazardous waste sites, for such exposure to occur.

Chronic-Duration Exposure and Cancer. No adverse health effects were seen in a long-term (20 years) inhalation study of 200 workers occupationally exposed to ethylbenzene (Bardodej and Cirek 1988). No chronic-duration dermal studies in animals were located in the literature. One chronic-duration inhalation study (NTP 1996) suggesting evidence of carcinogenicity in B6C3F$_1$ mice and F344/N rats and one chronic-duration oral study (Maltoni et al. 1985) reporting increases in malignant tumors were found. Studies that evaluate the effects of long-term exposures and provide quantitative exposure data would be useful as the potential exists for human populations to be exposed to ethylbenzene from contamination at hazardous waste sites, particularly from oral and inhalation exposures. The data are currently limited to the two studies listed above.

The carcinogenicity of ethylbenzene was investigated in three studies: an epidemiological study of humans occupationally exposed by inhalation (Bardodej and Cirek 1988), an inhalation exposure 2-year bioassay in rats and mice (NTP 1996), and an oral study using rats (Maltoni et al. 1985). The results of both the human epidemiological study and the oral study in rats were inconclusive, given the marked limitations present in both studies (e.g., possible simultaneous exposure to other chemicals in the human study; only one dose group used and no survival data in the animal study). However, the NTP study in rats and mice showed clear evidence of carcinogenicity in male rats, and some evidence of carcinogenicity in female rats and male and female mice (NTP 1996). No carcinogenicity studies following dermal exposure were located in the literature. Since dermal absorption can be a significant route of exposure to the liquid form of ethylbenzene, further studies of the dermal effects of ethylbenzene would be informative.

Genotoxicity. Available human data (Holz et al. 1995) indicate that ethylbenzene may be genotoxic. A weak induction of sister chromatid exchanges in human lymphocytes following ethylbenzene exposure was seen (Norppa and Vainio 1983a). Data are available regarding the genotoxic potential of ethylbenzene from *in vitro* assays in bacteria, yeast, and mammalian cell cultures (McGregor et al. 1988; NTP 1996). These data are summarized in Table 2-6. Although the results generally indicate that ethylbenzene is not genotoxic, marginal genotoxic effects have been reported in some tests. Independent confirmation or refutation of these studies, as well as further genotoxicity studies, especially in mammalian systems, would help provide clarification of these conflicting results. In particular, chromosome aberrations in occupationally exposed persons would provide useful information.

Reproductive Toxicity. No studies on reproductive effects of ethylbenzene by the inhalation or oral routes in humans and few studies using animals were located. The results from one animal study suggest that adverse reproductive effects may occur in animals following oral exposure to ethylbenzene (Ungvary 1986). No reduced fertility was reported in rats exposed to ethylbenzene by inhalation, but the possibility of this occurring was not ruled out. Additional reproductive studies, particularly for the inhalation and oral routes of exposure and involving multigenerational or continuous breeding studies, would help clarify the potential for ethylbenzene to cause adverse reproductive effects in humans.

Developmental Toxicity. No human data on developmental toxicity of ethylbenzene by any route are available. Minor birth defects have occurred in newborn rats, but not rabbits, whose mothers were exposed by breathing air contaminated with ethylbenzene (Andrew et al. 1981; Ungvary and Tatrai 1985). These defects consisted of urinary tract anomalies, and supernumerary ribs, a frequently observed indicator of

variation in the development of the skeletal system in rodents. Supernumerary ribs were observed in the presence of minimal maternal changes. A developmental MRL for intermediate-duration inhalation exposure was determined based on data from the rat study (Andrew et al. 1981). No studies were located that considered subtle developmental effects observed during postnatal development (e.g., behavioral or learning disability). In addition, no studies of postnatal exposure were found. These studies would be helpful in evaluating potential developmental effects in humans exposed to ethylbenzene via inhalation or ingestion. There are no available data concerning dermal exposure to ethylbenzene during development. Since it is possible that women and children may come in dermal contact with liquid ethylbenzene, these additional studies would be useful in more thoroughly evaluating the potential of ethylbenzene to cause developmental effects.

Immunotoxicity. No data are available regarding the immunotoxicity of ethylbenzene in humans or animals by the inhalation, oral, or dermal routes. There are some data to suggest that hematological effects may be seen, but these data are inconsistent (Cragg et al. 1989; NTP 1992). Inhalation and oral exposure studies would be most useful in confirming the potential of ethylbenzene to affect blood cells, since these routes are the major ways by which persons are exposed to ethylbenzene. Dermal sensitization tests may also provide useful data on the likelihood of an allergic response occurring since the potential for skin contact by humans occurs in the workplace and in soil and water at hazardous waste sites.

Neurotoxicity. Acute-duration inhalation studies in humans and animals exposed to ethylbenzene indicate that ethylbenzene causes neurological effects (Andersson et al. 1981; Molnar et al. 1986; Mutti et al. 1988; Romanelli et al. 1986; Tegeris and Balster 1994). Some data are available on possible mechanisms of action through dopamine depletion. No ethylbenzene-related behavioral changes were reported in one study (Yant et al. 1930), but other neurological parameters were not monitored. Studies have been conducted that investigated biochemical changes in the brains of animals following inhalation exposure, and some studies were located regarding histopathological changes following ethylbenzene exposure (Biodynamics 1986; Cragg et al. 1989). Well conducted acute-, intermediate-, and chronicduration studies including functional observation batteries, motor activity, and neurological evaluation across all exposure routes would be useful for confirming these data.

Epidemiological and Human Dosimetry Studies. The few available epidemiological studies on the health effects of ethylbenzene were primarily limited to occupational studies in which quantitative estimates of exposure were lacking and other limitations (e.g., multiple exposure routes, simultaneous

exposure to other hazardous chemicals) were present. Studies using volunteers exposed to low concentrations of ethylbenzene have provided useful information on effects of acute-duration inhalation exposure on the central nervous system (Yant et al. 1930). No studies were available in which humans were exposed orally or dermally to ethylbenzene. Further epidemiological studies conducted in the vicinity of hazardous waste sites containing ethylbenzene or in occupational settings where ethylbenzene is used would provide useful information on the health effects in humans. Data on lung function and neurological effects from these studies would be particularly valuable as these are likely to be targets of ethylbenzene toxicity.

Biomarkers of Exposure and Effect. Sensitive methods are available for determining ethylbenzene and ethylbenzene metabolites in biological tissues and fluids. However, limited data are available associating levels of ethylbenzene in human tissues and fluids with adverse health effects. Hematopoietic changes were shown to correlate with ethylbenzene concentrations in the blood. Additional animal or epidemiological studies evaluating the association between levels in tissue or fluids and adverse health effects would be useful to devise more sensitive and more specific early biomarkers of effect.

Exposure. Exposure to ethylbenzene can be monitored through levels of ethylbenzene in breath, bIood, or tissue, or levels of its metabolites, mandelic or phenylglyoxylic acid in urine. Both of these metabolites are considered to be specific to ethylbenzene (Ogata and Taguchi 1987). The Biological Exposure Index (BEI) for ethylbenzene is 1.5 g mandelic acid/g creatinine in urine (ACGIH 1996). Additional identification of biomarkers of exposure to ethylbenzene are not necessary at this time.

Effect. There are currently no known specific biomarkers of effect for ethylbenzene. Development of methods to identify biomarkers that would indicate toxic effects, and the extent of those toxic effects after exposure to ethylbenzene, would be helpful in managing health effects that occur after significant exposure to ethylbenzene.

Absorption, Distribution, Metabolism, and Excretion. Quantitative and qualitative evidence indicates that ethylbenzene is rapidly and efficiently absorbed by humans following inhalation and dermal exposures. Animal data support these findings and indicate that absorption rates are high following oral exposures as well.

Only one study (Engstrom and Bjurstrom 1978) is available that outlines the distribution of ethylbenzene in humans following inhalation exposure. This study indicates rapid distribution to adipose tissues

throughout the body. Numerous oral and inhalation studies in animals support these results. Ethylbenzene is accumulated primarily in the intestine, liver, kidney, and fat, which provides some basis for ethylbenzene-induced effects observed in the liver and kidney. No data on distribution of ethylbenzene following dermal exposure were located. Such information would be useful because absorption of liquid ethylbenzene via this route is rapid in humans and because the potential exists in humans for dermal exposure.

The metabolism of ethylbenzene in humans and animals has been studied. Although some differences in the metabolic pattern according to route of exposure, sex, nutritional status, and species have been documented, pharmacokinetic data show no significant differences in metabolism between oral and inhalation routes in either humans or animals. Further studies that correlate these differences in metabolism with differences in health effects would be useful. Data on metabolism following dermal exposure are sparse, because it is difficult to accurately measure absorption of volatile compounds. Additional data on metabolism following dermal exposure would be useful as these exposures could occur both from contaminated soil or groundwater.

Ethylbenzene has been shown to be rapidly eliminated from the body following inhalation exposure (primarily in the urine) in both humans and animals. These studies (Gromiec and Piotrowski 1984; Yamasaki 1984) are sufficient to characterize the elimination of ethylbenzene following inhalation exposure. A small number of studies in animals exposed orally and humans exposed dermally support these findings. Further studies on elimination of ethylbenzene via these exposure routes would be useful, especially because differences in the excretion patterns have been observed with different routes of exposure.

Comparative Toxicokinetics. Quantitative and qualitative variations in the absorption, distribution, metabolism, and excretion of ethylbenzene were observed depending on exposure routes, sex, nutritional status, and species, as previously outlined. Further studies that focus on these differences and their implications for human health would be useful. Additionally, *in vitro* studies using human tissue and physiologically based pharmacokinetic modeling would contribute significantly to the understanding of the kinetics of ethylbenzene, since they would provide information on half-lives and saturation kinetics associated with the metabolism of ethylbenzene.

Methods for Reducing Toxic Effects. No information was found that specifically addressed the reduction of toxic effects after absorption of ethylbenzene. Development of clinical procedures for

minimizing the effects of ethylbenzene on the respiratory, hepatic, and renal systems, and the central nervous system would be useful in situations where significant exposure had occurred.

Children's Susceptibility. There are no data describing the effects of ethylbenzene exposure in children or developing postnatal animals. Data needs relating to development are discussed in more detail above under developmental effects. In order to evaluate whether ethylbenzene presents a unique hazard to children, additional information on the health effects, pharmacokinetics, metabolism, and mechanism of action in children is needed. It is unknown whether children differ from adults in their susceptibility to health effects from exposure to ethylbenzene. Pharmacokinetic studies investigating whether ethylbenzene or its active metabolites cross the placenta or are transferred into breast milk would be useful. Studies to determine whether there are specific biomarkers of exposure in children would be helpful in monitoring the exposure of children to this chemical. In addition, information describing methods of reducing toxic effects and decreasing beody burden in children might be helpful. Child health data needs relating to exposure are discussed in Section 5.8.1, Data Needs: Exposures of Children.

2.11.3 Ongoing Studies

The toxicological significance of the metabolism of alkylbenzenes is currently being investigated by W.1. Backes (Louisiana State University). The objective of this project is to supply information that will aid in the identification of conditions under which individuals might be susceptible to alkylbenzene (including ethylbenzene) toxicity. No other ongoing studies regarding health effects of ethylbenzene exposure were identified in the available literature (FEDRIP 1996).

3. CHEMICAL AND PHYSICAL INFORMATION

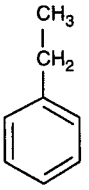
3.1 CHEMICAL IDENTITY

Ethylbenzene is an aromatic hydrocarbon that occurs naturally in petroleum and is a component of aviation and automotive fuels. It is used as a solvent and in the production of synthetic rubber and styrene. Information regarding the chemical identity of ethylbenzene is located in Table 3- 1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Ethylbenzene is a colorless liquid with an aromatic odor. Information regarding the physical and chemical properties of ethylbenzene is located in Table 3-2. Ethylbenzene is a flammable and combustible liquid. Vapors are heavier than air and may travel to a source of ignition and flash back. Liquid ethylbenzene floats on water and may travel to a source of ignition and spread fire. Combustion may produce irritants and toxic gases (NFPA 1994). Ethylbenzene may accumulate static electricity and will react with oxidizing materials (NFPA 1994).

Table 3-1. Chemical Identity of Ethylbenzene

Characteristic	Value	Reference
Chemical name	Ethylbenzene	Merck 1989
Synonyms	EB; ethyl benzene; ethylbenzol; phenylethane	HSDB 1995
Trade names	No data	
Chemical formula	C_8H_{10}	Merck 1989
Chemical structure		
Identification numbers:		
CAS Registry	100-41-4	Merck 1989
NIOSH RTECS	NIOSH/DAO700000	HSDB 1995
EPA Hazardous Waste	F003; Ethylbenzene	HSDB 1995
OHM/TADS	7216709	HSDB 1995
DOT/UN/NA/IMCO	UN 1175; Ethylbenzene	HSDB 1995
Shipping	IMO 3.2, Ethylbenzene	HSDB 1995
HSDB	84	HSDB 1995
NCI	NCI-C56393	HSDB 1995
STCC	49 091 63; Ethylbenzene	HSDB 1995

CAS = Chemical Abstracts Service; DOT/UN/NA/IMO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Databank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances; STCC = Standard Transport Commodity Code

Table 3-2. Physical and Chemical Properties of Ethylbenzene

Property	Values	References
Molecular weight	106.17	Lide 1994
Color	Colorless	Merck 1989
Physical state	Liquid	Merck 1989
Melting point	-95 °C	Lide 1994
Boiling point	136.2 °C	Lide 1994
Density at 20 °C/4 °C	0.8670	Lide 1994
at 25 °C/25 °C	0.866	Merck 1989
Odor	Sweet, gasoline-like	CHRIS 1985
Odor threshold:		
Water	0.029 mg/L	Amoore and Hautala 1983
	0.140 mg/L	Rosen et al. 1963; Verschueren 1983
Air	2.3 ppm	Amoore and Hautala 1983
	2–2.6 mg/m^3	Verschueren 1983
Solubility:		
Water at 0 °C	197 mg/L	Polak and Lu 1973
at 15 °C	140 mg/L	Verschueren 1983
at 20 °C	152 mg/L	Verschueren 1983
at 25 °C	160 mg/L	Amoore and Hautala 1983
at 25 °C	177 mg/L	Polak and Lu 1973
at 25 °C	208 mg/L	Bohon and Claussen 1951
Organic solvents	Miscible with usual organic solvents	Merck 1989
	Soluble in alcohol and ether	Lide 1994
Partition coefficients:		
Log K_{ow}	4.34	Mabey et al. 1982
	3.13	Yalkowsky and Valvani 1976
	3.15	Hansch and Leo 1979
Log K_{oc}	2.22 (calculated)	Chiou et al. 1983
	2.38 (measured)	Hodson and Williams 1988
	2.40 (calculated)	Vowles and Mantoura 1987
Vapor pressure		
at 20 °C	7 mm Hg	Verschueren 1983
at 25 °C	1.27 kPa (9.53 mm Hg)	Mackay and Shiu 1981
at 25.9 °C	10 mm Hg	Sax and Lewis 1989
at 30 °C	12 mm Hg	Verschueren 1983
at 74.1 °C	100 mm Hg	OHM/TADS 1988
Henry's law constant:		
at 20 °C	6.6x10^{-3} atm-m^3/mol	Mabey et al. 1982
at 20 °C	8.7x10^{-3} atm-m^3/mol	Lyman et al. 1982
at 25 °C	8.43x10^{-3} atm-m^3/mol	Mackay et al. 1979
at 25 °C	7.9x10^{-3} atm-m^3/mol	Mackay and Shiu 1981
Autoignition temperature	810°F (432°C)	NFPA 1994
Flash point	70°F (21°C)	NFPA 1994
Flammability limits	0.8 (lower) vol% – 6.7 (upper)vol%	NFPA 1994
Conversion factors	1 mg/m^3 = 0.23 ppm	Verschueren 1983
	1 ppm = 4.35 mg/m^3	

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Ethylbenzene is primarily produced by the alkylation of benzene with ethylene in liquid-phase slurry reactors promoted with aluminum trichloride catalysts or by vapor-phase reaction of benzene with dilute ethylene-containing feedstock with a boron trifluoride catalyst supported on alumina (EPA 1987c; HSDB 1995; Ransley 1984; Sandmeyer 1981). Other methods of manufacturing ethylbenzene include preparation from acetophenone, dehydrogenation of naphthenes, catalytic cyclization and aromatization, separation from mixed xylenes via fractionation, reaction of ethylmagnesium bromide and chlorobenzene, extraction from coal oil, and recovery from benzene-toluene-xylene (BTX) processing (HSDB 1995; Merck 1983; Ransley 1984; Sandmeyer 1981). Commercial grades of ethylbenzene may also contain small amounts of *m*-xylene, *p*-xylene, cumene, and toluene (HSDB 1995).

Ethylbenzene production in the United States has shown a steady increase from 1983 through 1994 (C&EN 1994a, 1994b, 1995a, 1995b). Production for this period was 7.9 (1983), 7.6 (1984), 7.4 (1985), 9.0 (1986), 9.3 (1987), 9.9 (1988), 9.2 (1989), 8.4 (1990), 11.4 (1991), 11.1 (1992), 11.8 (1993), and 11.9 billion pounds (1994) (C&EN 1994a, 1995a; USITC 1987, 1994). Ethylbenzene production capacity also increased slightly from 1988 to 1992. Annual U.S. production capacity reported for 1988, 1990, and 1992 was 9.5, 11.5, and 12.5 billion pounds, respectively (SRI 1988, 1990, 1992). More recent information on production capacity was not located (SRI 1994, 1995, 1996). In 1994, ethylbenzene was ranked 19th among the top 50 chemicals produced in the United States (C&EN 1995a).

Currently, there are 11 major producers of ethylbenzene in the United States. These producers include Amoco Corporation of Texas City, Texas; ARC0 Chemical Company of Channelview, Texas; Chevron Chemical Company of St. James, Louisiana; Cos-Mar Company of Carville, Louisiana; Deltech Corporation of Baton Rouge, Louisiana; Dow Chemical U.S.A. of Freeport, Texas; Huntsman Chemical Corporation of Bayport, Texas; Phibro Energy USA, Inc. of Houston, Texas; Rexene Corporation of Odessa, Texas; Sterling Chemical, Inc. Texas City, Texas; and Westlake Styrene Corporation of Lake Charles, Louisiana (SRI 1996). Of the 11 major U.S. producers currently manufacturing ethylbenzene, 4 companies including ARC0 Chemical Company, Cos-Mar Company, Sterling Chemicals, Inc., and Dow

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Chemical U.S.A. produce 20, 16, 13, and 13%, respectively, or a total of 62% of the ethylbenzene manufactured in the United States (SRI 1996).

Table 4- 1 lists the facilities in each state that manufacture or process ethylbenzene, the intended use, and the range of maximum amounts of ethylbenzene that are stored on site. There are currently 921 facilities that produce or process ethylbenzene in the United States. The data listed in Table 4-1 are derived from the Toxics Release Inventory (TR196 1998). These data should be used with caution however since only certain types of facilities are required to report (EPA 1995d). Therefore, this is not an exhaustive list.

4.2 IMPORT/EXPORT

In 1978 and 1981, $153x10^7$ kg (33.7 million pounds) and $2.09x10^7$kg (46.1 million pounds), respectively, of ethylbenzene were imported into the United States (HSDB 1995). More recently, U.S. imports of ethylbenzene have fluctuated greatly from 1991 through 1995 (USDOC 1996). Import volumes were $37x10^6$ kg (81.57 million pounds), $3.1x10^6$kg (6.83 million pounds), $5.3x10^6$ kg (11.68 million pounds), $35.5x10^6$ kg (78.26 million pounds), and $25.1x10^6$ kg (55.34 million pounds) for 1990, 1991, 1992, 1993, and 1994, respectively (USDOC 1996). Import volumes for ethylbenzene have been relatively small typically representing 1% or less of the annual domestic production volume.

U.S. exports of $8.59x10^7$ kg (189 million pounds), $4.84x10^7$ kg (106 million pounds), and $7.49x10^7$ kg (165 million pounds) were reported for 1978, 1983, and 1985, respectively (Bureau of the Census 1985; HSDB 1995). More recently, U.S. exports of ethylbenzene have steadily declined from 1991 to 1995 (USDOC 1996). Export volumes were $87x10^6$ kg (191 million pounds), $54.9x10^6$ kg (121 million pounds), $15.8x10^6$ kg (34.8 million pounds), $28.3x10^6$ kg (62.4 million pounds) and $9.5x10^6$ kg (20.9 million pounds) for 1990, 1991, 1992, 1993, and 1994, respectively (USDOC 1996). Export volumes for ethylbenzene have been relatively small typically representing 1% or less of the annual domestic production volume.

4.3 USE

Ethylbenzene is used primarily as a precursor in the production of styrene (ACGIH 1986; Merck 1983; Ransley 1984; Verschueren 1983). More than 99% of the ethylbenzene produced in 1984 was used in

Table 4-1. Facilities That Manufacture or Process Ethylbenzene

STATE [a]	NUMBER OF FACILITIES	RANGE OF MAXIMUM AMOUNTS ON SITE IN POUNDS [b]	ACTIVITIES AND USES [c]
AK	2	100000 - 9,999,999	1, 3, 4, 8
AL	26	100 - 99,999,999	1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 13
AR	18	100 - 999,999	1, 2, 3, 6, 7, 8, 11, 12, 13
AZ	2	100 - 9,999	8, 12, 13
CA	54	0 - 49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
CO	4	100 - 9,999,999	1, 4, 6, 8, 12, 13
CT	8	1000 - 999,999	2, 3, 4, 6, 8, 10, 11, 13
DE	3	10000 - 49,999,999	1, 2, 3, 7, 8, 9, 12, 13
FL	12	1000 - 999,999	7, 8, 10, 11, 12, 13
GA	20	100 - 999,999	1, 2, 3, 4, 6, 8, 9, 10, 11, 12, 13
HI	2	1000000 - 9,999,999	1, 2, 6, 8
IA	16	100 - 999,999	2, 3, 8, 9, 10, 11, 12, 13
IL	74	0 - 49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
IN	51	100 - 9,999,999	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13
KS	17	0 - 9,999,999	1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
KY	20	100 - 999,999	1, 2, 3, 4, 6, 8, 9, 10, 11, 12, 13
LA	41	1000 - 499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13
MA	5	1000 - 99,999	8, 10, 11, 12, 13
MD	9	1000 - 999,999	8, 9, 11, 12, 13
ME	2	1000 - 99,999	12, 13
MI	55	0 - 9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MN	15	1000 - 99,999,999	1, 3, 4, 6, 7, 8, 9, 10, 11, 12, 13
MO	31	100 - 999,999	7, 8, 9, 10, 11, 12, 13
MS	19	100 - 49,999,999	1, 6, 7, 8, 11, 12, 13
MT	4	100000 - 9,999,999	1, 3, 4, 6, 7, 8, 9, 13
NC	19	1000 - 999,999	1, 3, 5, 8, 11, 12, 13
ND	2	1000 - 9,999,999	1, 2, 3, 4, 7, 11
NE	5	100 - 99,999	8, 11, 12
NH	2	10000 - 99,999	8
NJ	28	1000 - 49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13
NM	5	100000 - 9,999,999	1, 3, 4, 6, 7, 8, 9, 13
NV	2	1000 - 99,999	8, 9
NY	15	100 - 99,999	8, 9, 11, 12, 13
OH	75	0 - 49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
OK	13	1000 - 49,999,999	1, 3, 4, 6, 7, 8, 9, 10, 11, 12
OR	6	1000 - 999,999	8, 10, 11, 12
PA	49	100 - 9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13
PR	6	100 - 999,999,999	1, 2, 3, 4, 5, 6, 8, 12, 13
RI	2	1000 - 9,999	11, 12, 13
SC	8	1000 - 99,999	8, 10, 11, 12, 13
SD	4	1000 - 9,999	8, 11, 12
TN	17	1000 - 9,999,999	1, 2, 6, 8, 9, 10, 11, 12, 13
TX	108	0 - 999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
UT	8	100 - 99,999,999	1, 3, 4, 7, 8, 9, 10, 11
VA	14	1000 - 999,999	1, 3, 5, 6, 7, 8, 9, 11, 12, 13
VI	1	10000000 - 49,999,999	1, 2, 3, 4, 7
VT	1	10000 - 99,999	8
WA	14	100 - 9,999,999	1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 13

Table 4-1. Facilities That Manufacture or Process Ethylbenzene (continued)

STATE [a]	NUMBER OF FACILITIES	RANGE OF MAXIMUM AMOUNTS ON SITE IN POUNDS [b]	ACTIVITIES AND USES [c]
AK	2	100000 - 9,999,999	1 , 3 , 4 , 8
WI	22	0 - 9,999,999	1 , 6 , 8 , 9 , 10 , 11 , 12 , 13
WV	15	1000 - 999,999	1 , 5 , 6 , 8 , 11 , 12 , 13
WY	6	1000 - 9,999,999	1 , 3 , 4 , 5 , 6 , 7 , 8 , 10 , 13

Source: TRI96 1998

[a] Post office state abbreviations used

[b] Range represents maximum amounts on site reported by facilities in each state

[c] Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses

styrene production, while the remainder was exported or sold in solvent applications (HSDB 1995). Minor uses of ethylbenzene include use as a solvent, as a constituent of asphalt and of naphtha, and in fuels (ACGIH 1986; Merck 1983; Verschueren 1983). Ethylbenzene is also used in the manufacture of acetophenone, cellulose acetate, diethylbenzene, ethyl anthraquinone, ethylbenzene sulfonic acids, propylene oxide, and a-methylbenzyl alcohol (HSDB 1995; Verschueren 1983).

4.4 DISPOSAL

Regulations governing the treatment and disposal of wastes containing ethylbenzene are detailed in Chapter 7. Recommended methods for the disposal of ethylbenzene include burial in a landfill and rotary kiln incineration, liquid injection incineration, and fluidized bed incineration (Bonner et al. 198 1; HSDB 1995; IRPTC 1985). Ethylbenzene may be disposed of by adsorbing it in vermiculite, dry sand, earth or a similar material and then by burial in a secured sanitary landfill or by atomizing in a suitable combustion chamber (IRPTC 1985). Ethylbenzene is a good candidate for liquid injection incineration at a temperature range of 650-1,600 °C and a residence time of 0.1 to 2 seconds; a candidate for rotary kiln incineration at a temperature range of 820-1 ,600 °C and a residence time of seconds for gases and liquids and hours for solids; and a good candidate for fluidized bed incineration at a temperature range of 450-980 °C and a residence time of seconds for gases and liquids, and longer for solids (HSDB 1995).

The following waste water treatment technologies have been investigated for disposal of ethylbenzene; biological treatment, air and steam stripping, or activated carbon treatment (HSDB 1995). Spent ethylbenzene solvents and still bottoms from the recovery of these solvents are designated hazardous wastes and, as such, are subject to RCRA handling and recordkeeping requirements (EPA 1981b).

According to the Toxics Release Inventory (TRI), in 1996, a total of 11,860,593 pounds (5.3 million kg) of ethylbenzene were released to the environment (air, water, land, and underground injection) from 921 large manufacturing and processing facilities (TR196 1998). In addition, an estimated 58,872 pounds (26,704 kg) were released by manufacturing and processing facilities to publicly owned treatment works (POTWs) and an estimated 15,400,453 pounds (7.0 million kg) were transferred offsite (TR196 1998). No additional information was located on the trends in disposal methods related to ethylbenzene.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Ethylbenzene is an aromatic hydrocarbon naturally present in crude petroleum. It is widely distributed in the environment because of human activities such as the use of fuels and solvents (which account for the bulk of emissions) and through chemical manufacturing and production activities. Because of its volatile nature, partitioning into the atmosphere from various environmental media is an important environmental fate process. Exposure to this chemical is thus most likely to occur by inhalation. However, it is also present in trace amounts in some water supplies. Thus, ingestion also may be an important exposure pathway in some cases. Exposures from contaminated water may also occur via inhalation and dermal absorption during showering and other household activities (Beavers et al. 1996).

Physical, chemical, and biological processes can remove ethylbenzene from the medium of concern and reduce human exposures. In the atmosphere, ethylbenzene, which exists predominantly in the vapor phase, is removed by partitioning into rainwater or by chemical transformations caused by the sun's energy (photooxidation) via reaction with hydroxyl radicals, which structurally alter the molecule. Photolytic transformations may also take place in surface water in the presence of naturally occurring hurnic materials (sensitized photolysis). Biologically induced transformations take place largely in soil and surface water in the presence of oxygen; however, anaerobic degradation can also occur in soil, sediment, and groundwater. Although chemical transformations can result in reduced exposures to ethylbenzene in the atmosphere, one toxic by-product of ethylbenzene photodegradation, peroxyacetylnitrate (PAN) may be of concern. Ethylbenzene, as well as a variety of other hydrocarbons, has been implicated in the atmospheric formation of PAN in smog (Yanagihara et al. 1977).

The kinetics of partitioning and/or transformation processes are site specific and depend upon many external factors. For example, the extent of biodegradation observed in an environmental medium depends upon the type and population of microorganisms present, the concentration of ethylbenzene, the presence of other compounds that may act as a substrate, and the presence or absence of oxygen. Biodegradation in soil will also compete with migration processes such as volatilization and infiltration to groundwater. Because ethylbenzene migration is only moderately retarded by adsorption onto soil, rapid transport of the

compound to an anaerobic environment (groundwater) before biotransformation in soil is possible and may allow ethylbenzene to persist in an aquifer.

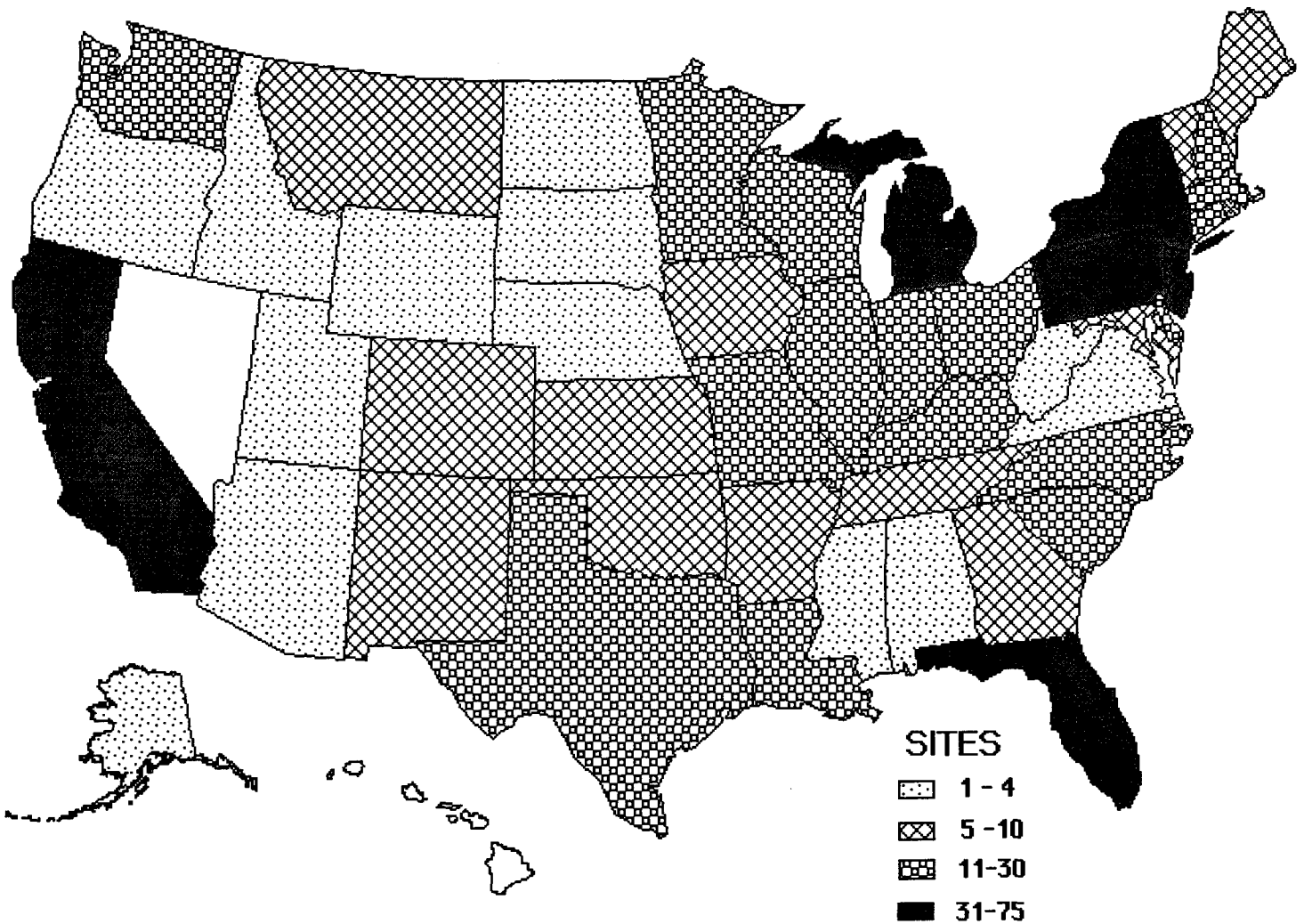
Although information is limited on dietary exposures, ethylbenzene does not appear to significantly bioaccumulate in aquatic or terrestrial food chains, and human exposure through this route is not likely to be of concern.

Exposure of the general population to ethylbenzene is possible through contact with gasoline, automobile emissions, solvents, pesticides, printing ink, varnishes, coatings, and paints. Cigarette smoke also has been identified as a source of exposure to this chemical. Ethylbenzene is widely present at low concentrations in rural, suburban, and urban atmospheres with the highest concentrations generally detected in areas of gasoline stations, tunnels, highways, and parking lots. Ethylbenzene is also typically present in indoor air at low concentrations (median = 1 ppb). Occupational exposures are expected within the petroleum industry; within industries using solvents, paints, and coatings; and during the manufacture and handling of ethylbenzene and styrene (which is manufactured from ethylbenzene).

Several groups within the general population may have potentially higher exposures to ethylbenzene by inhalation or by consumption of or dermal contact with contaminated drinking water or soil. These groups include individuals living near manufacturing and processing facilities, petroleum refineries, and hazardous waste disposal sites. Exposures associated with the consumption of contaminated drinking water as well as with inhalation and dermal exposure during showering and bathing in contaminated water would be expected for individuals that derive their primary drinking water supply from residential wells downgradient of uncontrolled landfills, hazardous waste sites, and leaking underground storage tanks that are contaminated with ethylbenzene. Individuals living near these sites may also be exposed via dermal contact with, or ingestion of soil contaminated with ethylbenzene.

Ethylbenzene has been identified in at least 731 of the 1,467 current or former EPA NPL hazardous wastes sites (HazDat 1998). However, the number of sites evaluated for ethylbenzene is not known. The frequency of these sites within the United States can be seen in Figure 5-1. Of these sites, 718 are located in the United States and 2 are located in the Commonwealth of Puerto Rico (not shown).

Figure 5-1. Frequency of NPL Sites with Ethylbenzene Contamination



Derived from HazDat 1998

5.2 RELEASES TO THE ENVIRONMENT

According to the Toxics Release Inventory (TRI), in 1996, a total of 27538,543 pounds (12,491,273 kg) of ethylbenzene was released to the environment from 95 1 large processing facilities (TR196 1998). Table 5-l lists amounts released from these facilities. Of the total release, an estimated 76,352 pounds (34,633 kg) were released by manufacturing and processing facilities to publicly owned treatment works (POTWs) and an estimated 17,733,077 pounds (8,043,588 kg) were transferred offsite (TR196 1998). The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1995d). Therefore, this is not an exhaustive list. Facilities are required to report data to TRI if they have 10 or more full-time employees, if the facility is classified under Standard Industrial Classification (SIC) codes 20 through 39, if the facility manufactures or processes more than 25,000 pounds of the chemical, or otherwise uses more than 10,000 pounds of the chemical in the calendar year (EPA 1995d).
Ethylbenzene has been identified in a variety of environmental media (air, soil gas, surface water, groundwater, leachate, soil, and sediment) collected at 731 of the 1,467 NPL hazardous waste sites (HazDat 1998). The frequency of these sites within the United States can be seen in Figure 5-l.

5.2.1 Air

The majority of ethylbenzene releases to the environment occur to the atmosphere. Because of its frequent use, and production in manufacturing operations, ethylbenzene is an important industrial chemical. In 1994, ethylbenzene was ranked 19th among the top 50 chemicals produced in the United States, with total production estimated to be almost 12 billion pounds (C&EN 1995a). Its release can occur during manufacturing, processing, and handling. In 1978, emissions of ethylbenzene in the United States from catalytic reformate production alone were estimated at over 2 million pounds (Fishbein 1985). Fuels and solvents, however, are considered to account for the bulk of emissions (Fishbein 1985). Gasoline contains approximately 2% (by weight) ethylbenzene, which is added as an anti-knocking agent (Mayrsohn et al. 1978 as cited in NAS 1980). Ethylbenzene has been measured from tail pipe emissions of gasolinepowered vehicles at a weighted average rate of 12 mg/km (considering both catalyst and noncatalyst equipped cars) (Hampton et al. 1983). Exposures to ethylbenzene can also occur while individuals are traveling in the passenger compartment of automobiles, and the chemical has been found at much higher concentrations during automobile engine malfunctions (Lawryk and Weisel 1996; Lawryk et al. 1995).

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Ethylbenzene

		Total of reported amounts released in pounds per year [a]						
STATE [b]	NUMBER OF FACILITIES	AIR [c]	WATER	LAND	UNDERGROUND INJECTION	POTW TRANSFER	OFF-SITE WASTE TRANSFER	TOTAL ENVIRONMENT [d]
AK	2	20,935	1	400	0	0	9	21,345
AL	26	254,092	1,000	0	0	250	373,496	628,838
AR	18	230,878	89	250	0	0	177,062	408,279
AZ	2	1,406	0	0	0	0	10,550	11,956
CA	53	61,082	22	280	250	7,314	420,563	489,511
CO	4	3,449	0	0	0	0	510	3,959
CT	8	8,658	333	0	0	1	121,438	130,430
DE	3	29,850	0	0	0	0	71,991	101,841
FL	12	147,452	0	0	0	307	304,669	452,428
GA	18	208,611	0	0	0	20	447,509	656,140
HI	2	4,308	0	255	0	0	395	4,958
IA	16	219,330	0	0	0	0	150,854	370,184
IL	74	292,442	399	898	0	5,737	1,830,466	2,129,942
IN	52	450,161	307	292	0	10	369,197	819,967
KS	17	169,415	35	0	0	5	144,118	313,573
KY	20	665,455	109	1,721	0	420	583,112	1,250,817
LA	41	306,031	621	530	2,099	76	217,752	527,109
MA	5	2,641	0	0	0	0	21,938	24,579
MD	9	112,806	6	0	0	77	124,454	237,343
ME	2	2,916	0	0	0	0	15,841	18,757
MI	54	1,215,104	0	0	0	2,947	4,033,468	5,251,519
MN	15	188,441	27	0	0	5	169,773	358,246
MO	30	897,437	0	0	0	757	593,269	1,491,463
MS	19	393,271	46	12	0	5	217,225	610,559
MT	4	21,450	9	5	0	5	1,078	22,547
NC	18	97,516	0	0	0	2,600	122,470	222,586
ND	2	14,674	0	0	0	0	528	15,202
NE	5	74,648	5	0	0	0	3,936	78,589
NH	2	41,882	0	0	0	0	2,050	43,932
NJ	28	102,897	153	0	0	387	680,200	783,637
NM	5	46,537	0	510	0	250	1,318	48,615

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Ethylbenzene (continued)

		Total of reported amounts released in pounds per year [a]						
STATE [b]	NUMBER OF FACILITIES	AIR [c]	WATER	LAND	UNDERGROUND INJECTION	POTW TRANSFER	OFF-SITE WASTE TRANSFER	TOTAL ENVIRONMENT [d]
NV	2	131	0	0	0	0	0	131
NY	15	94,489	65	0	0	5	309,826	404,385
OH	75	675,661	36	2,006	40	2,143	2,379,358	3,059,244
OK	13	130,924	48	36	0	209	68,517	199,734
OR	6	12,640	0	0	0	0	7,166	19,806
PA	49	248,275	264	2	0	10,526	799,691	1,058,758
PR	6	35,888	1,108	0	0	0	1,172,432	1,209,428
RI	2	13,460	0	0	0	0	3,100	16,560
SC	8	46,321	0	0	0	250	156,198	202,769
SD	4	39,339	0	0	0	0	18,904	58,243
TN	17	163,094	6	0	0	1,303	128,583	292,986
TX	107	757,335	641	53,662	333,538	38,958	1,019,155	2,203,289
UT	8	8,893	250	75	0	1,327	516	11,061
VA	14	334,907	721	0	0	39	31,098	366,765
VI	1	36,179	1	0	0	0	3,192	39,372
VT	1	905	0	0	0	250	250	1,405
WA	14	120,021	13	13	0	0	7,804	127,851
WI	22	160,632	0	0	0	169	338,806	499,607
WV	15	121,992	500	0	0	0	77,146	199,638
WY	6	37,422	260	877	5	0	96	38,660

Source: TRI96 1998

[a] Data in TRI are maximum amounts released by each facility

[b] Post office state abbreviations used

[c] The sum of fugitive and stack releases are included in releases to air by a given facility

[d] The sum of all releases of the chemical to air, land, and water, and underground injection wells; and transfers off-site by a given facility

POTW = publicly owned treatment works

Emissions from gasoline-powered vehicles were found to be somewhat higher than from diesel trucks (Hampton et al. 1983). Similarly, ethylbenzene has been measured in jet fuel emissions (Katzman and Libby 1975) and has been reported in waste incinerator stack emissions (Jay and Stieglitz 1995; Junk and Ford 1980). Most recently, ethylbenzene has been shown to be released into the atmosphere from volatile organic compound (VOC)-laden waste water in municipal sewer systems (Quigley and Corsi 1995).

Emissions of ethylbenzene can arise from transport of hot asphalt from a manufacturing plant to a paving site and from subsequent road paving operations. Kitto et al. (1997) measured the emissions of volatile organic compounds from Type I and Type II hot asphalts. At 150°C, the concentration of the ethylbenzene emissions from Type I asphalt was 800 μg/m^3; at 200°C, the concentration was 2,200 μg/m^3, an increase by a factor of 2.8. At 150°C, the concentration of the ethylbenzene emissions from Type II asphalt was 7000 μg/m^3; at 200°C, the concentration was 21,000 μg/m^3, an increase by a factor of 3.

Mukund et al. (1996) conducted chemical mass balance source apportionment modeling on a data set of 142 3-hour integrated air samples collected at six different sites in three separate campaigns during the summer of 1989 in Columbus, OH. The contributions (± standard error) from the sources considered, expressed as percentage of measured average concentration, were 55±11 from vehicle exhaust, 0.7&2 from gasoline vapor, 0±3 from natural gas, 20+4 from industrial solvents, and 0±1 from the drycleaning/ degreasing/wastewater composite source. These five sources contributed 76±12% of the measured average concentration of 1.1 μg/m^3.

Ethylbenzene releases to the air especially in indoor environments can occur with the use of consumer products such as pesticides, liquid process photocopiers and plotters, solvents, carpet glue, paints, varnishes, automotive products, adhesives, and fabric and leather treatments (Hodgson et al. 1991; Lillo et al. 1990; NAS 1980; Otson et al. 1994; Sack et al. 1992; Wallace et al. 1987b). Ethylbenzene (in addition to other aromatic hydrocarbons, such as benzene, styrene, and xylenes) has also been measured in cigarette smoke (Barrefors and Petersson 1993; Wallace et al. 1986, 1987c). A recent study of indoor air in a home using gasoline-contaminated drinking water found that exposures to ethylbenzene could occur via inhalation during showering and other household activities (Beavers et al. 1996). Ethylbenzene concentrations in shower air were often one to two orders of magnitude higher than non-shower air.

According to the TRI, in 1996, the estimated releases of ethylbenzene of 9,324,283 pounds (4,229,424 kg) to air from 951 large processing facilities accounted for about 33.9% of total environmental releases (TR196 1998). Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution, however, since only certain types of facilities are required to report (EPA 1995d). Therefore, this is not an exhaustive list.

Ethylbenzene has been identified in air and soil gas samples collected at 87 and 44 of the 731 NPL hazardous waste sites respectively, where it was detected in some environmental media (HazDat 1998).

5.2.2 Water

Releases to water can occur as a result of industrial discharges (Snider and Manning 1982), fuel spillage (Gschwend et al. 1982; Tester and Harker 198l), leaking petroleum pipelines or underground storage tanks (Cotruvo 1985), landfill leachate (Barker 1987; Beavers et al. 1996; Chen and Zoltek 1995; Hallbourg et al. 1992), and the inappropriate disposal of wastes containing ethylbenzene (Eiceman et al. 1986). Ocean releases occur as a result of offshore oil production, hydrocarbon venting, oil field brines, and tanker oil spills (Sauer et al. 1978). Sauer and Tyler (1995) recently reported that ethylbenzene was one of the most commonly detected VOCs in motor vehicle waste fluids released from routine vehicle maintenance shops entering catch basins and septic tanks in Wisconsin. Ethylbenzene was detected at a mean concentration of 11 ppb (range 3-98 ppb) in catch basin waste water, 1.5 ppb (range 7-23 ppb) in septic tank effluent, and 8 ppb (range 9-53 ppb) in septic tank sludge.

According to the TRI, in 1996, the estimated releases of ethylbenzene of 7,075 pounds (3,209 kg) to water from 95 1 large processing facilities accounted for less than 0.1% of total environmental releases (TR196 1998). However, 76,352 pounds (34,633 kg) were released indirectly to POTWs and some of this volume may have been released to surface water. Table 5-l lists amounts released from these facilities. The TRI data should be used with caution, however, since only certain types of facilities are required to report (EPA 1995d). This is not an exhaustive list.

Ethylbenzene has been identified in surface water, groundwater, and leachate samples collected at 115, 488, and 92 of the 731 NPL hazardous waste sites respectively, where it was detected in some environmental media (HazDat 1998).

5.2.3 Soil

Ethylbenzene can be released to soils through the spilling of gasoline and other fuels (Sauer and Tyler 1995; Tester and Harker 1981); through the disposal of solvents and household products such as paint, cleaning and degreasing solvents, varnishes, and pesticides; through emissions from leaking underground storage tanks (Cotruvo 1985), and leaching from landfill sites (Barker 1987).

According to the TRI, in 1996, the estimated releases of ethylbenzene of 61,824 pounds (28,043 kg) to soil from 951 large processing facilities accounted for about 0.2% of total environmental releases (TR196 1998). In addition, an estimated 335,932 pounds (152,376 kg) or 1.2% of total environmental releases were released via underground injection. Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution, however, since only certain types of facilities are required to report (EPA 1995d). This is not an exhaustive list.

Ethylbenzene has been identified in soil and sediment samples collected at 379 and 132 of the 73 1 NPL hazardous waste sites respectively, where it was detected in some environmental media (HazDat 1998).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The moderately high vapor pressure of ethylbenzene (Table 3-2) suggests a moderate to strong tendency for ethylbenzene to partition into the atmosphere where it will exist predominantly in the vapor phase (Eisenreich et al. 198 1; Mackay 1979; Masten et al. 1994). Depending upon site-specific conditions, releases to surface soil can result in substantial losses to the atmosphere in addition to subsurface infiltration. Since it has a moderately high vapor pressure, ethylbenzene will evaporate fairly rapidly from dry soil. Vapor phase transport will occur from subsurface releases (i.e., from leaking underground storage tanks) and during migration through unsaturated soil pore spaces (Rhue et al. 1988). This vapor phase migration is measured using soil gas sampling methods. Atmospheric reaction with hydroxyl radicals can limit the atmospheric ethylbenzene transport (Dewulf and van Langenhove 1997).

The high Henry's law constant (Table 3-2) which measures partitioning between water and air, indicates that a significant proportion of ethylbenzene will partition from water into air (Mackay 1979; Masten et al. 1994). Ethylbenzene dissolved in surface water, soil pore water, or groundwater will thus migrate into an available atmospheric compartment until its saturated vapor concentration is reached. Based on its K_{oc} value (Table 3-2) and using the classification scheme of Swann et al. (1983), ethylbenzene is classified as having moderate mobility in soils. Sorption and retardation by soil organic carbon content will occur to a moderate extent, but sorption is not significant enough to completely prevent migration in most soils. Particularly in soils with low organic carbon content, ethylbenzene will tend to leach into groundwater. Mobility is also possible in aquifers that contain very little solid-phase organic matter, a condition common to sand and gravel aquifers (Ptacek et al. 1984). Sorption and desorption experiments performed by Dewulf et al. (1996) demonstrated that the sorption process of ethylbenzene on marine sediments is reversible and that the sorption is even lower than expected from the log K_{ow} data and the organic carbon content of the sediment. They concluded that the marine sediment compartment is not an important sink for the VOCs investigated when they are brought into the environment.

When ethylbenzene is part of a complex mixture of hydrocarbons associated with a petroleum spill or leak, the proportion of ethylbenzene that will bind to soil versus the amount that will migrate toward groundwater depends primarily on the type of soil, the particular petroleum product in which the ethylbenzene is dissolved, the size of the spill, and the amount of rainfall (Stokman 1987). For example, the solubility of ethylbenzene varies in accordance with the presence of other petroleum products (Ptacek et al. 1984). While the pure compound solubility of ethylbenzene in water is 180 mg/L, its solubility in water equilibrated with JP-jet fuel is 10.6 mg/L (Burris and MacIntyre 1984). Potter (1993) also reported that the equilibrium aqueous solubility of ethylbenzene was 2.4 mg/L with gasoline, 0.18 mg/L with diesel fuel, and 0.007 mg/L with #6 fuel oil equilibrated with groundwater. Both of these authors calculated the solubility concentrations of ethylbenzene in water equilibrated with various petroleum products. In addition, solvent spills of chemicals such as ethylbenzene may enhance the mobility of other organic chemicals, which do strongly adsorb to soil (Rao et al. 1985). No information was found concerning bioavailability of ethylbenzene from soil for human dermal or oral uptake.

Boyd et al. (1990) reported that corn residues absorbed a significantly greater amount of ethylbenzene as compared with surface soil. The authors suggested that the highly lipophilic plant cuticle appears to be the

sorptive component. Kango and Quinn (1989) also reported that humic acid adsorbed higher amounts of ethylbenzene and xylenes ranging from 40 to 77 times greater than soil.

Once in the atmosphere, ethylbenzene will be transported until it is removed by physical or chemical processes. Physical removal processes, which involve partitioning into clouds or rainwater, are relevant to ethylbenzene, which has been measured in Los Angeles rainwater (Kawamura and Kaplan 1983). The concentrations of several dissolved organic chemicals in rainwater and in the atmosphere during rainfall events were measured by Ligocki et al. (1985). The authors found that the concentration of ethylbenzene in rainwater was approximately equal to the inverse of the dimensionless Henry's law constant (Table 3-2) at atmospheric temperatures. This indicates that ethylbenzene is removed from the atmosphere through precipitation, but it can re-enter the atmospheric environment upon evaporation.

In comparison to chemicals such as polychlorinated biphenyls (PCBs), DDT, and other chlorinated pesticides, which are of great concern with respect to bioaccumulation, ethylbenzene does not significantly bioaccumulate in aquatic food chains. A bioconcentration factor (BCF) in fish of 37.5 based on a log K_{ow} of 3.15 has been estimated (EPA 1980). A 3% weighted average lipid content in fish and shellfish was assumed by EPA in the calculation. The calculated BCF is a theoretical value based on known constants, and is a conservative estimate of the bioconcentration of this chemical in fish. A calculated BCF of 167 was also estimated for fathead minnows *(Pimephales promelas)* (ASTER 1995). In a shellfish study, the ethylbenzene concentration in clam tissue was 5 times higher than that measured in water after an 8-day continuous-flow exposure to the water-soluble fraction of Cook Inlet crude oil (Nunes and Benville 1979).

Ethylbenzene has also been found to partition into human tissues, primarily as a result of inhalation exposures (see Section 5.5). Ethylbenzene has been detected in human adipose tissue (Section 2.3.2. l), blood (Sections 2.2.1 and 2.3.1), and in breast milk (Sections 2.6 and 2.7.1). No information was located concerning the bioavailability of ethylbenzene from contaminated soil or sediment either with respect to dermal exposure or oral intake via consumption of soil particles from unwashed hands.

5.3.2 Transformation and Degradation

5.3.2.1 Air

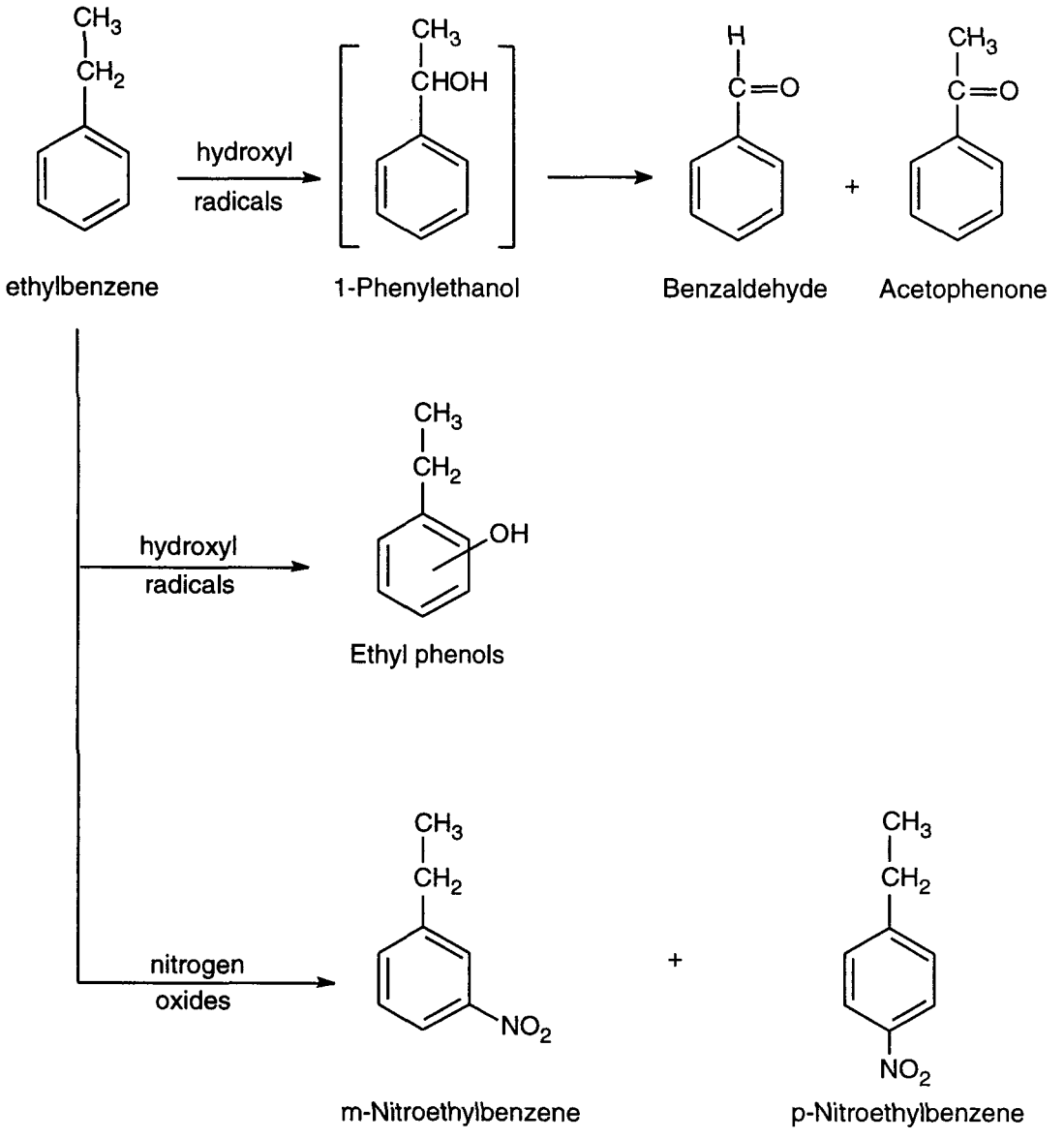
Ethylbenzene undergoes atmospheric transformations through reaction with photolytically generated hydroxyl radicals (Atkinson et al. 1978; Ohta and Ohyama 1985; Ravishankara et al. 1978), NO_3 radicals (Atkinson et al. 1987), and atomic oxygen (Grovenstein and Mosher 1970; Herron and Huie 1973). Gas phase reactions with ozone and structurally similar molecules such as toluene have been observed (Atkinson and Carter 1984). Reactions with hydroxyl radicals appear to be of most importance, and a chemical lifetime of 35 daylight hours for ethylbenzene has been estimated (Atkinson et al. 1978). An atmospheric half-life of 2.7 days (65 hours) was estimated using the Atmospheric Oxidation Program (SRC 1995). Degradation appears to be somewhat faster (half-life of 5.5 hours) in summer than in winter (halflife 24 hours) (Ravishankara et al. 1978; Singh et al. 198l), and faster under photochemical smog conditions (Dilling et al. 1976). Oxidation by-products from the reaction with hydroxyl radicals and nitrogen oxides include ethylphenols, benzaldehyde, acetophenone, and *m*- and *p*-nitroethylbenzene (Hoshino et al. 1978). The major degradation pathways for ethylbenzene in the atmosphere are summarized in Figure 5-2.

Experiments conducted with various hydrocarbons on the formation of photochemical aerosols or the haze associated with smog revealed that aromatics such as ethylbenzene produced only low yields of aerosol when compared with more reactive compounds such as alkenes (O'Brien et al. 1975). The formation of peroxyacetylnitrate (PAN) is related to the photoreactivity of the reacting hydrocarbon. The photoreactivity of ethylbenzene is intermediate relative to other atmospheric hydrocarbons, and it is less reactive than gasoline, toluene, and alkenes such as propene (Yanagihara et al. 1977).

5.3.2.2 Water

In surface water, transformations of ethylbenzene may occur through two primary processesphotooxidation and biodegradation. Although ethylbenzene does not directly absorb light wavelengths that reach the troposphere, it is capable of undergoing photooxidation in water through an indirect reaction with other light-absorbing molecules, a process known as sensitized photolysis. The compounds 1-methylphenyl ketone (acetophenone), 1-phenylethanol, and benzaldehyde were identified from the laboratory

Figure 5-2. Major Degradation Pathways for Ethylbenzene in the Atmosphere



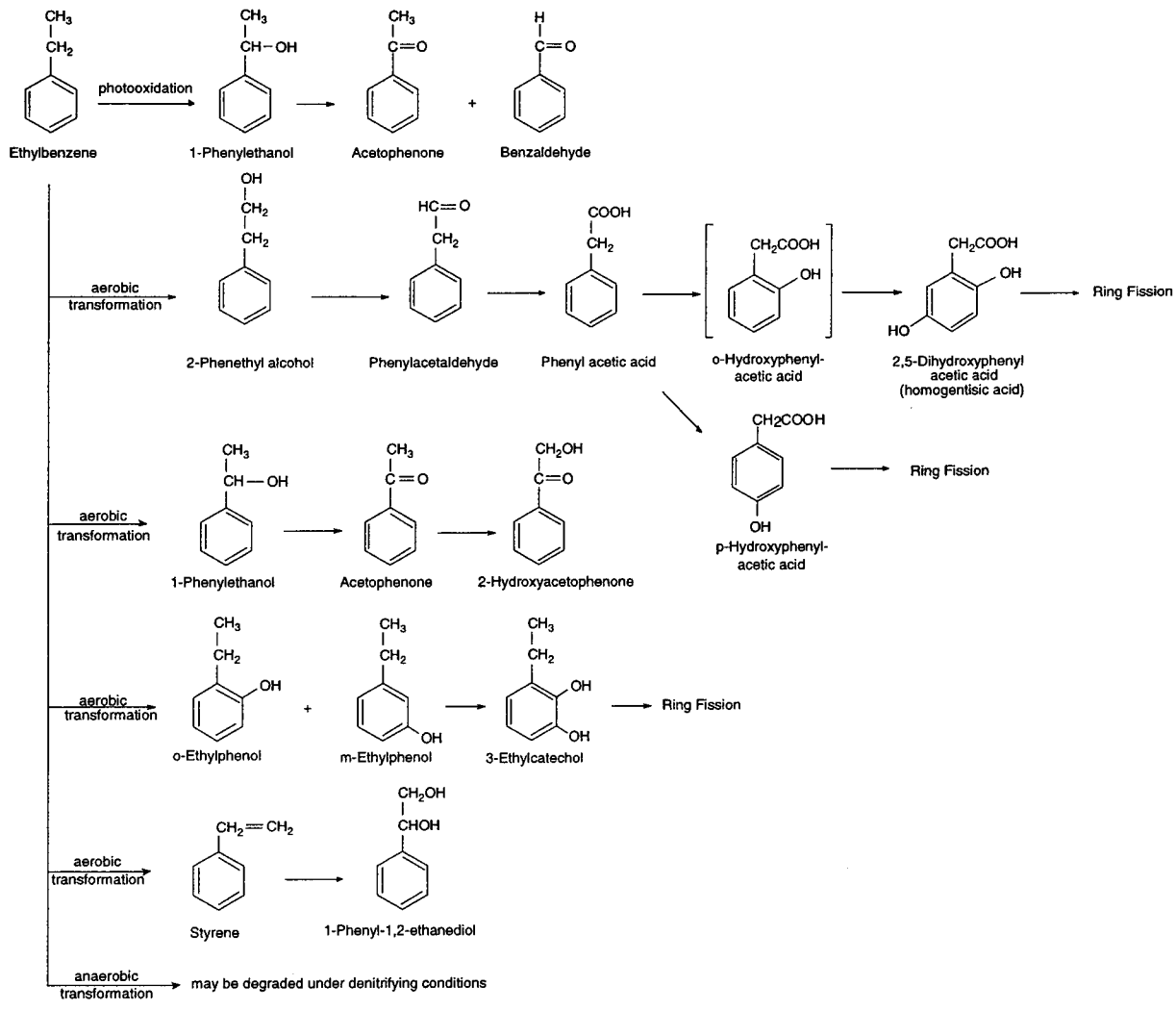
Source: Hoshino et al. 1978

photooxidation of ethylbenzene in both distilled water and seawater with acetophenone used as a sensitizer (Ehrhardt and Petrick 1984). In the environment, similar degradation is expected to occur in the presence of ubiquitous, naturally occurring humic material sensitizers. The major degradation pathways for ethylbenzene in water are summarized in Figure 5-3.

Biodegradation in aerobic surface water will compete with sensitized photolysis and transport processes such as volatilization. Volatilization and biodegradation of ethylbenzene in seawater have been observed by Gschwend et al. (1982), Masten et al. (1994), and Wakeham et al. (1983). Migration from surface water to subsurface soil with low amounts of oxygen or to aquifers with lower microbial populations, however, will limit the rate of transformation. No significant disappearance of ethylbenzene during 11 weeks of incubation with bacteria under low oxygen (anoxic) conditions was observed by Bouwer and McCarty (1983). Slow degradation of ethylbenzene was reported in anaerobic aquifer materials known to support methanogenesis, although a long acclimation period or lag time was required (Wilson et al. 1986). Less than 1% of the initial concentration of ethylbenzene remained after 120 weeks, indicating that, given sufficient time, ethylbenzene will be essentially completely biodegraded.

Laboratory microcosm tests were conducted to determine optimum conditions for ethylbenzene biodegradation by aquifer microorganisms under denitrifying condition (Hutchins 199 1). Ethylbenzene was degraded to below 5 μg/L when present as a sole source substrate and stoichiometric calculations indicated that nitrate removal was sufficient to account for 70 to 80% of the compound being mineralized. Biodegradation did not occur without the presence of nitrate, and nitrate removal was minimal without the presence of the ethylbenzene over a 55-day incubation period. In a laboratory microcosm containing aquifer material and groundwater from the North Bay site in Ontario, Canada, no significant loss of ethylbenzene was observed compared to unamended controls over a period of 187 days. In another experiment conducted at the North Bay site that used in *situ* biodegradation columns, ethylbenzene was completely degraded in at least 1 of the 8 in situ columns in less than 100 days (Acton and Barker 1992). In all cases, the authors attributed the ethylbenzene attenuation to biodegradation by methanogenic and fermentative bacteria. In another study using a laboratory scale flow-through aquifer column system, low dissolved oxygen (<l mg/L) conditions were initiated with the nitrate-amended column influent in order to mimic contaminated groundwater Fonditions distal from a nutrient injection well (Anid et al. 1993). The authors reported that 40% of the ethylbenzene was removed after several months of operation. In a similar study, using batch incubations seeded with 4 different aquifer materials, ethylbenzene was not degraded within

Figure 5-3. Major Degradation Pathways for Ethylbenzene in Water, Sediment, and Soil



Sources: Ehrhardt and Petrick 1984; Van DerLinden and Thijsse 1965; Burback and Perry 1993; Lee and Gibson 1996

4 months in any of the denitrifying enrichments tested, even though nitrate reduction occurred. Burback and Perry (1993) reported than Mycobacterium vaccae can catabolize a number of major groundwater pollutants, including ethylbenzene. At a concentration of 100 ppm ethylbenzene was not measurably degraded; however, at 50 ppm, 80% of the added ethylbenzene was degraded. A product peak of 4-ethylphenol was detected as well as a small amount of I-phenylethanol.

The contrast between biodegradation rates in the presence or absence of oxygen was demonstrated by a biofilm reactor study designed to simulate an aquifer (Bouwer and McCarty 1984). Continuous-flow laboratory column studies under aerobic and methanogenic conditions were performed with mixed bacterial cultures on glass beads. In the aerobic biofilm column, 99% of the ethylbenzene initially present was degraded within a 20minute detention time, while under methanogenic (anaerobic) conditions, only 7% was degraded within a 2-day detention time.

5.3.2.3 Sediment and Soil

Biodegradation of ethylbenzene by aerobic soil microbes has been reported by various researchers. The common soil microorganism *Pseudomonas putidu* is able to utilize ethylbenzene as a sole source of carbon and energy (Fukuda et al. 1989; Gibson et al. 1973). In some instances, co-oxidation or co-metabolism was observed (i.e., ethylbenzene was degraded by *Nocurdiu* sp. in the presence of other compounds that are more readily metabolized by the microorganism) (Jamison et al. 1970; Van der Linden and Thijsse 1965). Yadav and Reddy (1993) reported that the white-rot fungus *Phanerochaete chrysosporium* efficiently degraded ethylbenzene as well as other benzene, toluene, ethylbenzene and xylenes (BTEX) compounds when these chemicals were added either individually or as a composite mixture. In addition, substantially greater degradation of all the BTEX compounds was observed in static rather than in shaken liquid cultures. Furthermore, degradation was greater at 25°C than at 37°C, but pH variations between 4.5 and 7 had little effect on the extent of the degradation. Chen and Taylor (1995) reported that 2 thermophilic bacterial strains, *Thermus uquuticus* and an unidentified *Thermus sp.* degraded ethylbenzene (in a mixture with other BTEX chemicals) by 18% after 45 days of incubation at 70°C and by 32% after 45 days of incubation at 60°C respectively. Zappi et al. (1996) reported that ethylbenzene degraded rapidly in a pilot scale bioslurry reactor under aerobic conditions. The initial concentration (0.35 mg/kg) was degraded by 94% in 2 days.

Biotic transformations by aerobic soil microbes involve oxidation of the ethyl side chain to form phenylacetic acid (Van Der Linden and Thijsse 1965) and 1-phenylethanol (Bestetti and Galli 1984 as cited in ECETOC 1986); ring hydroxylation to form 2,3-dihydroxy-1-ethylbenzene (Gibson et al. 1973), 2-hydroxyphenlacetic acid, 4-hydroxyphenylacetic acid, and 2,5- and 3,4-dihydroxyphenylacetic acid (Van der Linden and Thijsse 1965); and ultimate ring cleavage to form straight chain carboxylic acids such as fumaric and acetoacetic acids (Van der Linden and Thijsse 1965). The major degradation pathways for ethylbenzene are summarized in Figure 5-3.

Anaerobic degradation of ethylbenzene based on observations from studies conducted under anaerobic conditions in other media and as discussed above (Bouwer and McCarty 1983, 1984; Wilson et al. 1986), would be much slower than that observed under aerobic conditions. Ramanand et al. (1995) studied the biodegradation of several organic pollutants including ethylbenzene in soil columns under denitrifying conditions. These authors reported that one of the significant factors governing biodegradation is the availability of suitable electron acceptors. The biodegradation of ethylbenzene, toluene, and xylenes has been demonstrated in laboratory samples obtained from subsurface habitats or in pure cultures under dinitrifying conditions (Hutchins 1991; Hutchins et al. 1991). Ramanand et al. (1995) reported that soil column bacteria, after sufficient acclimation time, metabolized 100-500 μM of toluene and ethylbenzene in less than 6 days under denitrifying conditions. These compounds were successfully degraded under anoxic conditions by the addition of nitrate and by stimulating the indigenous soil denitrifying bacteria.

The kinetics of biodegradation appear to be site specific, and depend upon factors such as the type and population of microbes present, the environmental temperature, the concentration of ethylbenzene, the presence of other compounds that may act as a substrate, and the amount of oxygen and electron acceptors present. Biodegradation in soil will also compete with migration processes such as volatilization and infiltration to groundwater.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to ethylbenzene depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on ethylbenzene levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The

analytical methods available for monitoring ethylbenzene in various environmental media are detailed in Chapter 6.

5.4.1 Air

Ambient air levels of 'volatile organic compounds, including ethylbenzene, were monitored as a part of a multi-media study known as the Lower Rio Grande Valley Environmental Scoping Study. Monitoring was preformed at a "central" site and at a "border" site in the Brownsville, Texas, air shed in the spring and summer of 1993. The median ambient concentration of ethylbenzene at the central site was 0.8 $\mu g/m^3$ (n=22; range=0.2-1.7 $\mu g/m^3$) in the spring and 0.4 $\mu g/m^3$ (n=14; range=0.2- 1 .0 $\mu g/m^3$) in the summer. These concentrations are either lower or comparable to those found in previous EPA and other monitoring investigations (Ellenson et al. 1997). The median indoor concentration of ethylbenzene for nine Ria Grande Valley residences measured in the spring was 1.00 $\mu g/m^3$ compared to a median outdoor concentration of 0.70 $\mu g/m^3$; in the summer, the median indoor concentration of ethylbenzene for five residences was 1.40 $\mu g/m^3$ compared to a median outdoor concentration of 0.35 $\mu g/m^3$ (Mukerjee et al. 1997).

An update of the 1980 National Ambient Volatile Organic Compounds (VOC) database prepared for EPA summarized concentrations of ethylbenzene by site type (Shah and Heyerdahl 1988). Median values are reported because they are less biased by a few high or low concentrations and, thus, may better represent the data than would average values. The median indoor concentration of ethylbenzene detected at 95 locations was 1 ppb (mean 2.9 ppb), while personal air monitoring of 1,650 individuals found a median concentration of 1.3 ppb (mean 3.2 ppb).

Of particular interest is that personal air monitoring of indoor air found higher concentrations of ethylbenzene than those observed in outdoor air. This was also observed during the Total Exposure Assessment Methodology (TEAM) Study conducted by EPA between 1979 and 1985 in an effort to measure exposures to 20 VOCs in personal air, outdoor air, and drinking water. The major cause for the higher personal air concentrations was felt to be the presence of ethylbenzene sources in the home. In the TEAM study, tobacco smoke was reported to be a main source of exposure to volatile aromatic compounds such as ethyl-benzene (Wallace et al. 1987a, 1987c). Based on the results of a stepwise regression carried out on data collected during the fall in New Jersey from 352 participants, overnight geometric mean ethylbenzene exposures of persons living in homes with smokers were approximately 1.5 times the geometric mean

exposures of persons living in homes without smokers. The amount of ethylbenzene measured in mainstream smoke of a single cigarette containing 16 mg of tar and nicotine was 8 l..tg (Wallace et al. 1987c). More recently, Wallace et al. (1989) reported that a maximum outdoor air concentration of ethylbenzene of 7.4 μg/m^3 was detected in 9 outdoor samples collected at each of 3 houses while maximum indoor air concentrations at these same residences ranged from 5 to 110 μg/m^3. Mean personal exposures averaged 28 μg/ m^3 (range 4.6-144 μg/ m^3) and the personal/outdoor ratio for ethylbenzene was 16.

The poor quality of indoor air has been linked to a number of symptoms (headache; nausea; irritation of the eyes, mucous membranes, and respiratory system; drowsiness; fatigue; and general malaise) which has been defined as "sick building" syndrome. Most recently, Kostiainen (1994) identified over 200 VOCs in the indoor air of 26 normal houses. Ethylbenzene was detected in 100% of the houses studied at an average concentration of 3.2 μg/m^3 (median 2.41 μg/m^3, minimum 0.62 μg/ m^3, and maximum 10.54 μg/ m^3 concentration). The median concentration of ethylbenzene (2.41 μg/ m^3) in these normal houses was lower in all but one case than ethylbenzene concentrations detected in houses with "sick building" syndrome where the concentrations ranged from 2.25 to 747.24 μg/m^3.

A nationwide study of indoor air concentration of 26 VOCs was conducted in Canada in 1991 (Fellin and Otson 1994). These authors reported that mean indoor ethylbenzene concentrations were 6.46 μg/m^3 (winter), 8.15 μg/m^3 (spring), 4.35 μg/m^3 (summer), and 13.98 μg/m^3 (fall) and that the concentrations declined with an increase in ambient air temperature. At ≤0, 0-15, and ≥15°C, the mean ethylbenzene concentration was 12.76, 7.78, and 6.46 μ/m^3, respectively. These authors concluded that indoor sources of ethylbenzene (primarily from household products) are likely to have a more significant influence on indoor air concentrations than climatic variables.

Concentrations of ethylbenzene were measured in soil gas, and indoor and outdoor air of a home located near a landfill in California (Hodgson et al. 1992). During the first sampling in September, ethylbenzene concentrations were not detected in soil gas or outdoor air, but were detected at 0.6 ppb in basement air. In October, ethylbenzene concentrations averaged 3.3 ppb in soil gas, 0.8 ppb in basement air, and 0.7 ppb in bedroom air. In this study, the authors found that the existence of soil gas contamination alone is not sufficient to result in significantly elevated indoor exposures. The entry rate of ethylbenzene and VOCs form the soil into the house was low. The limited entry that occurred at the conditions of the study was apparently the result of diffusive and advective flux of VOC through the cement blocks used in the

basement wall construction. The authors suggest that there is a general need to identify variables associated with residential sites with the highest potential for significantly elevated indoor exposures resulting from soil gas contamination.

Indoor VOC concentrations were analyzed in 12 California office buildings as part of the California Healthy Building Study (Daisey et al. 1994). These authors reported that ethylbenzene was detected at a geometric mean of 0.5 μg/m^3 (range 0.27-0.98 μg/m^3). These authors also reported that an estimated 82% of indoor air concentrations were contributed from motor vehicle emissions. Hodgson et al. (199 1) reported that concentrations of ethylbenzene in indoor air of a new office building ranged from 7 to 18.7 μg/m^3 over the course of a 14 month sampling period. Furthermore, ethylbenzene indoor air concentrations were higher than those in outdoor air and that the dominant source of VOCs in the building was liquid-process photocopiers and plotters which emitted a characteristic mixture of C_{10},-C_{11} isoparaffmic hydrocarbons.

Wadden et al. (1995) reported average VOC concentrations for indoor air monitored in a sheetfed offset printing shop. These authors reported mean ethylbenzene concentrations ranging from 0.27 to 0.84 mg/m^3 based on 12 1-hour samples.

Levels of ethylbenzene monitored in ambient air show great variation (Jonsson et al. 1985). Generally, air concentrations are much lower in rural areas than in urban areas, where vehicle emissions are thought to be a major contributor of ethylbenzene to ambient air. Ethylbenzene concentrations range from below detection limits in rural areas to 23.1 ppb on busy urban streets (Jonsson et al. 1985). Kelly et al. (1994) reported a median concentration of ethylbenzene of 1.1 μg/m3 (0.25 ppb) for 8,723 samples collected from 93 locations throughout the United States.

An update of the 1980 National Ambient VOCs database prepared for the EPA summarized concentrations of ethylbenzene by site type (Shah and Heyerdahl 1988). Median values are reported because they are less biased by a few high or low concentrations and thus may better represent the data than would average values. Median concentrations for 6 remote and 122 rural locations are reported as 0.156 and 0.013 ppb, respectively. Higher median concentrations were reported for 886 suburban (0.62 ppb) and 1,532 urban (0.62 ppb) locations. The daily median concentration of ethylbenzene considering all site types (including

source dominated [median 0.85 ppb] and workplace air [median 0.28 ppb]) was 0.60 ppb. Table 5-2 lists some monitoring results reported for ethylbenzene in various cities.

Ethylbenzene concentrations at four locations along U.S. Highway 70 near Raleigh, North Carolina, during the month of May were reported to range from 10 to 16 ppb (corrected to include upwind concentrations) (Zweidinger et al. 1988).

Concentrations of ethylbenzene were measured in two tunnels; the Fort McHenry Tunnel in Baltimore, Maryland (June 18-24, 1992) and the Tuscarora Mountain Tunnel in Pennsylvania (September 2-8, 1992) (Zielinska et al. 1996). These authors reported minimum and maximum concentrations for the Fort McHenry Tunnel of 6.3 and 89.2 ppb (on a carbon basis) for bore #3, respectively, and 0.5 and 114.1 ppb (on a carbon basis) for bore #4, respectively, and concentrations for the Tuscarora Tunnel of 1.2 and 11.1 ppb (on a carbon basis), respectively. The total number of light-duty vehicles (LDV) and heavy-duty vehicles (HDV) that passed through each tunnel was 12,273 LDV and 187 HDV for bore #3 and 11,788 LDV and 2,417 HDV for bore #4 of the Fort McHenry Tunnel and 4,887 LDV and 1,041 HDV for the Tuscarora Tunnel.

Ethylbenzene and other VOCs have been found to be removed from waste water in municipal sewers and were emitted to the ambient atmosphere prior to entering a downstream waste water treatment facility in Toronto, Ontario (Quigley and Corsi 1995). These authors measured concentrations of ethylbenzene during 4 monitoring events and found that concentrations ranged from not detectable to 5 ppm. Headspace concentrations of ethylbenzene exhibited a significant weekday/weekend trend. Significant emissions of all VOCs monitored occurred during three of the four monitoring events. Ethylbenzene had the second highest emissions during all periods and ranged from 7 to 14 g/hour (62-130 kg/year) for event 1 and from 1 to 13 g/hour (9-115 kg/year) for event 2. Ethylbenzene emissions at 5 municipal treatment facilities ranged from 0.08 to 93 g/day (0.003-3.9 g/hour). Results of this study suggest that sewers that accept VOC-laden waste water, and that are characterized by significant ventilation and drop structures, can be significant sources of VOC emissions (including ethylbenzene) relative to municipal waste water treatment facilities.

Assmuth and Kalevi (1992) reported that ethylbenzene was detected in municipal solid waste landfill gas at minimum and maximum concentrations ranging from 6.6 to 7.6 mg/m^3, <0.1 to 9.6 mg/m^3, 0.2 to 1.2 mg/m^3, and 85 to 98 mg/m^3 at 4 different landfill sites in Finland. Concentrations of ethylbenzene

Table 5-2. Ethylbenzene Concentrations in Ambient Air Samples Collected in the United States

Location	Concentration	Comments	Reference
Downey, CA	4.6±3.7 ppb (mean±S.D.) 16.1 ppb[a]	February 18–27, 1984; n=100	Singh et al. 1985
Los Angeles, CA	3–12 ppb (range)	September 29–November 13, 1981	Grosjean and Fung 1984
Riverside, CA	1.3±0.8 ppb (mean±S.D.) 4.0 ppb[a]	July 1–13, 1980; n=100	Singh et al. 1985
Denver, CO	2.2±3.1 ppb (mean±S.D.) 18.5 ppb[a]	June 15–28, 1980; n=100	Singh et al. 1985
Chicago, IL	0.8±1.2 ppb (mean±S.D.) 9.5 ppb[a]	April 20–May 2, 1981; n=100	Singh et al. 1985
St. Louis, MI	0.6±0.5 ppb (mean±S.D.) 2.1 ppb[a]	May 29–June 9, 1980 n=100	Singh et al. 1985
Camden, NJ	0.17 ppb (mean)	July 6–August 16, 1981; n=35	Harkov et al. 1983
Elizabeth, NJ	0.26 ppb (mean)	July 6–August 16, 1981; n=37	Harkov et al. 1983
Newark, NJ	0.33 ppb (mean)	July 6–August 16, 1981; n=38	Harkov et al. 1983
Staten Island, NY	1.7±2.5 ppb (mean±S.D.) 17.2 ppb[a]	March 26–April 5, 1981; n=100	Singh et al. 1985
Staten Island, NY	2.7±4.2 ppb (mean±S.D.) 16.7 ppb[a]	April 25–May 1, 1984; n=100	Singh et al. 1985
Philadelphia, PA	0.8±0.8 ppb (mean±S.D.) 7.3 ppb[a]	April 4–22, 1983 n=100	Singh et al. 1985
Pittsburgh, PA	0.8±1.6 ppb (mean±S.D.) 10.5 ppb[a]	April 7–17, 1981; n=100	Singh et al. 1985
Houston, TX	1.5±1.6 ppb (mean±S.D.) 8.2 ppb[a]	March 8–17, 1984; n=100	Singh et al. 1985
Jones State Forest, TX	2.8 ppb[b]	January 4–6, 1978	Seila 1979

[a]Maximum measured concentration
[b]Median concentration in 10 bag samples (median concentration in 5 can samples was 1.0 ppb)

n = number of samples; S.D. = standard deviation

measured in a biogas collection system at the Miron Quarry Municipal Waste Landfill Site in Montreal, Quebec ranged from 2 to 36 mg/m^3 (Goldberg et al. 1995).

Ethylbenzene has been detected in air and soil gas samples collected at 87 and 44 of the 720 NPL hazardous waste sites respectively, where it has been detected in some environmental media (HazDat 1998).

5.4.2 Water

The median ethylbenzene concentration in ambient surface waters in the United States in 1980-82 was less than 5.0 μg/L (ppb) according to EPA's STORET water quality database (Staples et al. 1985). The chemical was detected in 10% of the 1,101 samples collected during that period. Ethylbenzene was also detected in 7.4% of the 1,368 industrial effluent samples collected during 1980-82 at a median concentration of less than 3.0 μg/L (ppb).

From 1989 to 1993, New York City municipal wastewaters were analyzed to determine the frequency of detection of organic priority pollutants, including ethylbenzene (Stubin et al. 1996). Ethylbenzene was detected in 14 of 84 (17%) influent samples at concentrations ranging from 1 to 11 μg/L (ppb) and in only 1 of 84 (1%) effluent samples at a concentration of 2 μg/L (ppb).

Ethylbenzene and other VOCs have been detected in waste water in municipal sewers prior to entering a downstream waste water treatment facility in Toronto, Ontario (Quigley and Corsi 1995). These authors measured concentrations of ethylbenzene in waste water during several monitoring events and found that concentrations ranged from 0.059 to 0.086 mg/L (ppm) in one event and from 7 to 11 mg/L (ppm) in another event. The authors also determined that the stripping efficiency across two drop structures with waste water fall heights of 1 A-3 meters within the sewer system removed 3 l-36% of the ethylbenzene in the waste water. Results of this study suggest that sewers that accept VOC-laden waste water, and that are characterized by significant ventilation and drop structures, can be significant sources of VOC emissions (including ethylbenzene) relative to municipal waste water treatment facilities.

As part of EPA's Nationwide Urban Runoff Program, ethylbenzene was measured in 4% of the municipal runoff samples collected in 15 cities throughout the United States (Cole et al. 1984). The measured ethylbenzene concentration range was 1-2 μg/L (ppb).

Ethylbenzene was measured in seawater at an average concentration of 0.011 μg/L (ppb) and a concentration range of 0.0018-0.022 μg/L (ppb) over a 15month observation period at Vineyard Sound, Massachusetts (Gschwend et al. 1982). Ethylbenzene also has been reported in surface waters of the Gulf of Mexico at a concentration range of 0.0004-0.0045 μg/L (ppb) (Sauer et al. 1978).

Ethylbenzene has been detected in a relatively remote location (Mt. Mitchell, North Carolina) in cloud water at a mean concentration of 170 ng/L (range 0-450 ng/L) (Aneja 1993). The average ram concentration of ethylbenzene was 34 ng/L.

From 1989 to 1990 and from 1992 to 1993, ethylbenzene was monitored in wetland-treated leachate water at a municipal solid waste landfill in central Florida (Chen and Zoltek 1995). During the first sampling period, ethylbenzene was detected in surface water samples ranging from 0.06 to 0.09 ppb, and in groundwater samples ranging from 0.06 to 9.75 ppb. During the second sampling period (1992-93), ethylbenezene was not detected in surface water samples, but was detected in groundwater samples at concentrations ranging from below detection limits to 10.55 ppb. Ethylbenzene was detected in a study of three landfills in central Florida (Hallbourg et al. 1992). These authors reported the concentration of ethylbenzene in groundwater ranging from 1.63 to 9.75, <l to 83.8, and <l to 8.6 μg/L at the 3 different landfill sites. The mean concentration of ethylbenzene detected in landfill leachate from these disposal areas was 17.5 μg/L.

Ethylbenzene does not appear to be widespread in groundwater used for public drinking water supplies. Ethylbenzene was measured in all three drinking water plants sampled as part of the New Orleans Area Water Supply Study conducted by EPA in 1974 (EPA 1985b). The reported concentrations were 1.6, 1.8, and 2.3 μg/L (ppb). The 1982 Ground Water Supply Survey conducted by EPA reported ethylbenzene in only 3 out of 466 random samples at a mean concentration of 0.8 μg/L (ppb) and a maximum concentration of 1.1 μg/L (ppb) (Cotruvo 1985). Chemical monitoring in Wisconsin of over 1,174 public groundwater supplies revealed that ethylbenzene was detected in only 3 community wells (Krill and Sonzongni 1986). The concentration of ethylbenzene detected did not exceed the recommended Wisconsin

drinking water health advisory limit of 1,400 μg/L (ppb) in any of the community wells tested. Ethylbenzene was detected in public drinking water in Rhode Island with concentrations ranging from 1 μg/L to 3 μg/L (ppb) (RIDH 1989). Most recently, ethylbenzene was listed as one of the 58 most frequently detected chemical associated with groundwater contamination (Knox and Canter 1994). Ethylbenzene was listed as having a medium priority with respect to its frequency of occurrence.

Although public underground water supplies do not appear to be significantly affected by releases of ethyl-Benzene private residential wells near landfills, waste sites, or gas stations may be at risk. For example, ethylbenzene has been detected in wells downgradient from landfills in Southern Ontario at concentrations ranging from 12 to 74 μg/L (ppb) (Barker 1987). Chemical monitoring in Wisconsin of 617 private groundwater supplies revealed that ethylbenzene was detected in 12 private wells (Krill and Sonzongni 1986). The concentration of ethylbenzene detected exceeded the state's recommended drinking water advisory limit of 1,400 μg/L (ppb) in 9 of the 12 private wells tested.

Borden and Yanoschak (1990) compared ground and surface water quality impacts associated with North Carolina sanitary landfills. These authors found that ethylbenzene was detected at = 25% of the waste water effluents (receiving secondary treatment) and only 3% of the groundwater sampled in the vicinity of sanitary landfill sites. Groundwater monitoring at 479 hazardous waste disposal sites revealed that ethylbenzene, like the other 9 VOCs monitored, was detected at more than 100 of the 479 sites tested (Plumb 1991). Ethylbenzene was also one of the VOCs detected in groundwater samples from hazardous waste sites in all 10 EPA regions. Rosenfeld and Plumb (1991) reported that ethylbenzene was detected in groundwater at 19% of wood-treatment industry sites based on its frequency of detection and average concentration. Groundwater near an underground coal gasification site in northeastern Wyoming contained concentrations of ethylbenzene ranging from 92 to 400 μg/L (ppb) (Stuermer et al. 1982). Groundwater samples near a fuel spill in the Great Ouse Basin in Great Britain contained ethylbenzene concentrations as high as 1,110 μg/L (ppb) (Tester and Harker 1981).

Ethylbenzene has been detected in surface water, groundwater, and leachate samples collected at 115,488, and 92 of the 720 NPL hazardous waste sites respectively, where it has been detected in some environmental media (HazDat 1998).

5.4.3 Sediment and Soil

The median ethylbenzene concentration (dry weight) detected in sediment in the United States in 1980-82 was 5 μg/kg (ppb) according to EPA's STORET water quality database (Staples et al. 1985). The compound was detected in 11% of 350 sediment samples analyzed. No other recent quantitative information on ethylbenzene concentrations in soil or sediment were found. Ethylbenzene has been detected in soil and sediment samples collected at 379 and 132 of the 720 NPL hazardous waste sites respectively, where it has been detected in some environmental media (HazDat 1998).

5.4.4 Other Environmental Media

Ethylbenzene is not included in the FDA Market Basket Surveys, and little information on concentrations of the compound in foodstuffs is reported in the literature. Trace concentrations of ethylbenzene have been reported in split peas (0.013 mg/kg [ppm]), lentils (0.005 mg/kg [ppm]), and beans (mean concentration 0.005 mg/kg [ppm]; maximum concentration 0.011 mg!kg [ppm]) (Lovegren et al. 1979). Ethylbenzene was reported as one of 227 organic chemicals present in roasted filbert nuts (Kinlin et al. 1972). Most recently, Gorna-Binkul et al. (1996) reported concentrations of ethylbenzene in orange peel (0.0236 μg/g [ppm] dry weight) and in parsley leaves (0.2567 μg/g [ppm] dry weight). The author reported that the differences in concentrations of the VOCs was dependent on the plant species and the morphological part of the plant analyzed. In underground parts (i.e., roots and bulbs) not directly exposed to polluted ambient air during growth, no VOC concentrations were detected. Biedermann et al. (1995) reported concentrations of several VOCs in extra virgin olive oil collected in northwest Italy. These authors found ethylbenzene levels in raw olives of 6 μg/kg (ppb) which increased with time as they were milled to 25 μg/kg (ppb). Levels in the finished olive oils ranged from 11 to 27 μg/kg (ppb) depending on the method used. These authors reported that while some of the ethylbenzene was accumulated in the olives in the orchards, a larger proportions was accumulated as a result of exposure of the oil to air in the milling areas. Ethylbenzene concentrations in olive oil increased from 6 to 235 ppb after 2 days of exposure. The authors concluded that the production process increased the concentration of ethylbenzene in the oil as a result of uptake from the air which was likely to be contaminated with gasoline vapors associated with small vehicles used to move the olives from area to area within the olive oil mill.

Ethylbenzene was also found to migrate from thermoset polyester cooking containers (composed of crosslinking chains of styrene) into belly pork during cooking (Gramshaw and Vandenburg 1995). Migration ranged from <6 to 34 μg/kg for ethylbenzene. The authors also found that the migration measured during the second use of the cookware was generally higher than that during the first use. These authors also reported that ,ethylbenzene concentrations in food cooked in foil-covered dishes was higher than that in the same food cooked uncovered. This was especially true for ethylbenzene that was more volatile than the styrene tested. Ehret-Henry et al. (1994) also reported migration of ethylbenzene from polystyrene containers into dairy products. Concentrations of ethylbenzene ranged from 2 to 4 μg/kg for yogurt and 4 μg/kg for chocolate dessert.

Sack et al. (1992) conducted a survey of VOCs in 1,159 household items, including automotive products, household cleaners and polishes, paint related products, fabric and leather treatments, cleaners for electronic equipment, oils, greases, and lubricants, adhesive-related products, and miscellaneous products. Ethylbenzene was detected in 157 of 658 (24%) of the products tested. The highest mean ethylbenzene concentrations and percentage of products in each category in which ethylbenzene was detected are as follows; 7.2% w/w (wet weight) in 7.5% of automotive products, 2.4% w/w in 47.8% of paint-related products, and 1.0% w/w in 11.8% of fabric and leather treatments.

Hodgson et al. (1996) determined the contribution of environmental tobacco smoke (ETS) to concentrations of VOCs in smoking environments. These authors reported that the average emission factor for ethylbenzene for 6 brands of cigarettes was 101 μg/cigarette (range 83-142 μg/cigarette). The average concentration of ethylbenzene in 5 smoking areas ranged from 1.3 to 8.7 pg!m3 (0.3-2 ppb). Martin et al. (1997) determined the ETS yield of selected analytes, including ethylbenzene, for the 50 top-selling U.S. cigarette brand styles in 1991 and for the University of Kentucky Research cigarette, KlR4F. The ETS was generated by smokers in an environmental test chamber. The ethylbenzene concentrations measured were 8.68 μg/m^3 for full flavor cigarettes, 8.24 μg/m^3 for full flavor low tar cigarettes, and 8.72 μg/m^3 for ultra-low-tar cigarettes. The mean ethylbenzene concentration for all cigarettes was 8.50 pg/m3. The mean ethylbenzene yields by tar category weighted by market share were 8 1.18 μg/cigarette for full flavor cigarettes, 76.79 μg/cigarette for full flavor low tar cigarettes, and 8 1.66 μg/cigarette for ultra low tar cigarettes. The mean ethylbenzene yield for all cigarettes was 79.57 pg/cigarette.

Ethylbenzene was not detected (at a detection limit of 0.025 mg/kg [ppm] wet weight) in any of the 97 biota samples collected from all STORET stations in 1980-83 (Staples et al. 1985). Ethylbenzene was detected at low concentrations (0.0008 mg/g [0.8 ppm]) in oyster tissue, but not in clam tissue from Lake Pontchartrain at Passes, Louisiana (Ferrario et al. 1985). The highest average ethylbenzene concentration of 0.01 mg /kg [ppm] body weight was measured in the tissue of bottomfish from Commencement Bay in Tacoma, Washington (Nicola et al. 1987).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The highest exposure to ethylbenzene for the general public is most likely to occur via inhalation associated with the use of self-service gasoline pumps or while driving a gasoline-powered motor vehicle especially in high traffic areas or in tunnels (Lawryk et al. 1995). Backer et al. (1997) performed a study that measured exposures associated with the pumping two different blends of fuel under cold conditions in Fairbanks, Alaska. They found that the people in the study had significantly higher levels of gasoline components in their blood after pumping gasoline than before. The changes in VOC levels in blood were similar whether the individuals pumped regular or oxygenated gasoline. Before pumping regular gasoline, the median concentration of ethylbenzene in blood was 0.10 ppb (n=26) with a range of 0.02-0.73 ppb; after pumping, the median concentration was 0.16 ppb with a range of 0.06-l .40 ppb. Before pumping an oxygenated fuel blend that was 10% ethanol, the median concentration of ethylbenzene in blood was 0.11 ppb (n=22) with a range of 0.04-0.55 ppb; after pumping the ethanol blend, the median concentration was 0.16 ppb with a range of 0.06-0.64 ppb.

Lawryk and Weisel(1996) measured in-vehicle concentrations of selected gasoline-derived volatile organic compounds on 113 commutes through suburban New Jersey and 33 New Jersey/New York commutes. In a typical suburban commute, the mean in-vehicle concentration of ethylbenzene was 11.5±18.8 $\mu g/m^3$ (n=52) under low ventilation conditions and 8.5±11.2 $\mu g/m^3$ (n=43) under high ventilation conditions. On the New Jersey turnpike and in the Lincoln Tunnel, the mean in-vehicle concentrations of ethylbenzene were 8.8±10.8 $\mu g/m^3$ (n=32) and 14.3±0.2 $\mu g/m^3$ (n=32), respectively.

Ethylbenzene is ubiquitous in urban and rural atmosphere resulting from vehicular and industrial emissions (Shah and Heyerdahl 1988). Tobacco smoke also provides a general source of exposure to ethylbenzene in indoor air (Wallace et al. 1987c). Wallace et al. (1989) also reported that two activities; painting and the

use of automotive products (carburetor cleaner) led to increased indoor exposure to ethylbenzene by 100-fold. Information on exposure from foods is limited, but is not likely to be a significant source of ethylbenzene for the general population.

One-half of the household drinking water used in the United States is supplied by groundwater, and contamination of groundwater by petroleum products is an increasingly common problem (Beavers et al. 1996). Beavers et al. (1996) conducted a study in a New England household that used groundwater contaminated by gasoline from a leaking underground storage tank. A total daily dose of 379 μg ethylbenzene (204 μg ingested and 175 μg inhaled) was estimated for an exposed subject compared to a median daily dose of 32 μg for unexposed subjects. Of the 17.5 μg inhaled by the exposed subject, 108 μg was attributed to shower activities. The exposed subject and the three non-exposed subjects all were smokers.

The 1982 National Human Adipose Tissue Survey conducted by EPA measured ethylbenzene in 96% of the 46 composite samples analyzed for VOCs (Stanley 1986). A wet tissue concentration range of not detected (detection limit=2 ng/g) to 280 ng/g (ppb) was reported, but an average concentration was not provided.

Ethylbenzene has been detected in breast milk samples collected from 8 of 12 women from various cities in the United States; however, the concentrations were not reported (Pellizzari et al. 1982). The 12 women sampled in the study were residents of Bayonne, New Jersey (6 women), Jersey City, New Jersey (2 women), Bridgeville, Pennsylvania (2 women), and Baton Rouge, Louisiana (2 women).

Ashley et al. (1994) reported blood concentrations of selected VOCs in a reference group of nonoccupationally exposed individuals in the U.S. population. These authors reported a mean ethylbenzene concentration of 0.11 ppb (median 0.06 ppb; 95 percentile value of 0.48 ppb) for 631 individuals. In an earlier study (Ashley et al. 1992), these authors reported a mean ethylbenzene concentration of 0.12 ppb in 13 blood samples. Hajimiragha et al. (1989) conducted a study of 13 non-smokers and 1,4 smokers with no known occupational or hobby-related exposure to volatile organic hydrocarbons. These authors reported a mean and median ethylbenzene concentration of 65 1 ng/L (0.65 1 ppb) and 431 ng/L (0.431 ppb) for the non-smokers and 837 ng/L (0.837 ppb) and 533 ng/L (0.533 ppb) for the smokers. Ethylbenzene concentrations tended to occur at higher concentrations in the blood of smokers than in non-smokers;

however, the difference was not significant. Ashley et al. (1995) also reported that smoking elevated the blood levels of ethylbenzene and was highly correlated with blood levels of 2,5dimethylfuran. These authors reported a mean concentration of 0.10 ng/mL (ppb) (median 0.048 ng/mL; range from below detection limit to 2.7 ng/mL) for non-smokers and a mean concentrations of 0.17 ng/mL (ppb) (median 0.16 ng/mL; range 0.036-0.88 ng/mL) for smokers. To aid in understanding the kinetics of uptake and elimination of volatile organics (including ethylbenzene), Ashley and Prah (1997) measured blood concentrations before, during, and after exposure of five individuals to a mixture of volatile organics in a controlled chamber. The half-lives of the compounds measured were less than 1/2 hour, but the elimination time courses were multiexponential and suggested that, with repeated exposure, bioaccumulation may occur in humans.

Occupational exposure to ethylbenzene in the petroleum industry has been reported in a study that measured ethylbenzene concentrations in air for 49-56 workers during the summer of 1984 (Rappaport et al. 1987). The average air concentrations of ethylbenzene measured over the full work shift for gasoline service station attendants, transport drivers, and outdoor refinery personnel were comparable at 0.063, 0.079, and 0.079 mg/m^3, respectively (14.5, 18.2, and 18.2 ppb, respectively). The authors noted that exposures of service station attendants were significantly lower when vapor recovery systems were present. Personal air monitoring of 35 varnish workers (spraymen) has revealed an average ethylbenzene concentrations of 4.0 ppm, while the average concentration in blood was 61.4 µg/L (Angerer and Wulf 1985). Concentrations of ethylbenzene were monitored in auto paint shops in Spain that used organic solvents (Medinilla and Espigares 1988). These authors reported air concentrations of ethylbenzene ranging from 0.5 to 125.0 mg/m^3 (0.12-28.75 ppm).

The indoor air of screen printing plant workrooms located directly below houses in Amsterdam Holland was found to contain median TWA concentrations of ethylbenzene ranging from <0.03 mg/m^3 (7 ppb) to 1.30 mg/m^3 (299 ppb) and maximum TWA concentrations ranging from 0.11 mg/m^3 (25 ppb) to 3.21 mg/m^3 (739 ppb) (Verhoeff et al. 1988).

Spray-painting and gluing operations can also result in exposure to ethylbenzene; personal air monitoring of workers measured average exposures of approximately 0.5 ppm (2.18 mg/m^3) (Whitehead et al. 1984). Most of the operations measured during the study were performed in ventilation hoods.

5. POTENTIAL FOR HUMAN EXPOSURE

A recent survey of U.S. manufacturers of ethylbenzene conducted by the Styrene and Ethylbenzene Association (SEBA) indicated that typical workplace exposure levels of ethylbenzene in styrene and/or ethylbenzene processing plants were in the range of 0.1-1 ppm for an 8-hour TWA (Helmes 1990). Holz et al. (1995) reported that ethylbenzene air concentrations detected from air sampling in all areas of a styrene production facility located in the former German Democratic Republic ranged from 365 to 2,340 μg/m3 (0.08-0.53 ppm).

According to the National Occupational Exposure Study (NOES) conducted by NIOSH from 1981 to 1983, an estimated 201,838 workers were potentially exposed to ethylbenzene in the workplace (NIOSH 1991). The NOES database does not contain information on the frequency, concentration, or duration of occupational exposure to any of the chemicals listed. The survey provides only estimates of the numbers of workers for whom potential exposure in the workplace is an issue.

The Occupational Safety and Health Administration (OSHA) has set a Permissible Exposure Limit (PEL) based on a TWA of 100 ppm (≈435 mg/m^3) in the workplace (OSHA 1974). The American Conference of Governmental Industrial Hygienists also recommends a Threshold Limit Value (TLV-TWA) of 100 ppm (≈435 mg/m^3) for occupational exposures (ACGIH 1992). The recommended exposure limit (REL) for occupational exposures (TWA) set by the National Institute for Occupational Safety and Health is also 100 ppm (≈435 mg/m^3) for ethylbenzene based on a lo-hour average workday and a 40-hour workweek (NIOSH 1992).

5.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in Section 2.6, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, and breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior

and lifestyle also influence exposure. Children crawl on the floor; they put things in their mouths; they may ingest inappropriate things such as dirt or paint chips; they spend more time outdoors. Children also are closer to the ground, and they do not have the judgement of adults in avoiding hazards (NRC 1993).

Children can be exposed to ethylbenzene by inhalation in urban and rural atmospheres contaminated by vehicular and industrial emissions. Tobacco smoke also provides a general source for exposure of children to ethylbenzene in indoor air, especially in the homes where one or both parents smoke. Some household activities, such as painting, can lead to short-term exposures to higher levels of ethylbenzene if ventilation is inadequate. The limited information available on exposure from foods indicates that food is not likely to be a significant source of ethylbenzene for children. Ethylbenzene is heavier than air, and since young children are closer to the ground or floor because of their height, during accidental exposures they may be exposed to more ethylbenzene vapors than adults.

No studies were found that involved body burden measurements on children, and no levels of ethylbenzene or its metabolites were found for amniotic fluid, meconium cord blood or neonatal blood. Ethylbenzene has been detected in breast milk samples collected from 8 of 12 women from various cities in the United States; however, the concentrations were not reported (Pellizzari et al. 1982). The 12 women sampled in the study were residents of Bayonne, New Jersey (6 women), Jersey City, New Jersey (2 women), Bridgeville, Pennsylvania (2 women), and Baton Rouge, Louisiana (2 women). No direct pharmacokinetic experiments have been done to investigate whether significant amounts of ethylbenzene are transferred to breast milk in mammals.

Although no data were found in the literature, it is possible that children playing near hazardous waste sites could be dermally exposed to ethylbenzene in soil or orally exposed by hand-to-mouth activity and/or soil pica. Ethylbenzene, however, is only moderately adsorbed by soil. Since it has a moderately high vapor pressure, it will evaporate fairly rapidly from dry soil. However, under certain soil conditions, ethylbenzene may persist for longer periods of time; it has been detected in soil samples collected at 379 of the 720 NPL hazardous waste sites where it has been detected in some environmental media (HazDat 1998). No information was found concerning dermal and oral bioavailability of ethylbenzene in soil. In the home, intentionally sniffing solvents could lead to high levels of exposure. No information was found concerning differences in the weight-adjusted intakes of ethylbenzene by children.

No exposures of children to ethylbenzene by contamination of workers' homes were found in the Workers' Home Contamination Study conducted under the Worker's Family Protection Act (DHHS 1995).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to ethylbenzene (see Section SS), there are several groups within the general population that may receive potentially high exposures (higher than background levels) to ethylbenzene. These populations include individuals living in proximity to sites where ethylbenzene is produced or used in manufacturing or sites where ethylbenzene is disposed, and includes individuals living near the 73 1 NPL hazardous waste sites where ethylbenzene has been detected in some environmental media (HazDat 1998).

Individuals living or working near petroleum refineries or chemical manufacturing plants may receive higher inhalation exposures than those experienced by the general population. Residents living in the vicinity of gasoline stations, high traffic areas, tunnels, parking lots, and highways may also receive a higher than average inhalation exposure since ethylbenzene is a component of gasoline. Ethylbenzene has been detected in air at 87 of the 731 NPL hazardous waste sites where the chemical has been identified in some environmental media. Residential wells downgradient of leaking underground storage tanks, landfills, and hazardous waste sites contaminated with petroleum products and solvents may contain high levels of ethylbenzene. If these residential wells are the primary source of drinking water, this may pose a risk to human health via consumption of contaminated water as well as increased inhalation of and dermal contact with ethylbenzene during showering and bathing. A recent study of indoor air in a home using gasoline-contaminated drinking water found that exposures to ethylbenzene could occur via inhalation during showering and other household activities (Beavers et al. 1996). Ethylbenzene concentrations in shower air were often one to two orders of magnitude higher than non-shower air. These authors reported a total daily household dose of ethylbenzene of 379 μg, with 204 μg derived from ingestion of drinking water and 175 yg derived from inhalation (108 μg from shower-related inhalation and 67 μg from non-shower-related inhalation) to the exposed subject living in the home. The daily dose of ethylbenzene for an unexposed smoker by comparison was estimated to be 32 μg. Ethylbenzene has been detected in groundwater at 488 of the 731 NPL hazardous waste sites where the chemical has been identified in some environmental media.

5.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ethylbenzene is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of ethylbenzene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of ethylbenzene are well characterized (see Table 3-2) and allow prediction of the transport and transformation of the compound in the environment (Amoore and Hautala 1983; Bohon and Claussen 1951; Chiou et al. 1983; Hansch and Leo 1979; Hodson and Williams 1988; Mabey et al. 1982; Mackay and Shiu 1981; Polak and Lu 1973; Sutton and Calder 1975; Verschueren 1983). No additional studies are needed at the present time.

Production, Import/Export, Use, Release, and Disposal. Ethylbenzene has numerous uses (ACGIH 1986; Merck 1983; Ransley 1984; Verschueren 1983), and production of the chemical has steadily increased since 1983 (C&EN 1994a). Releases occur from a variety of common sources including manufacturing and production (TR196 1998), fuels, automobile exhaust, and fumes from paints, varnishes, solvents, carpet glue, and hot asphalt (Fishbein 1985; Hampton et al. 1983; Junk and Ford 1980; Katzman and Libby 1975; Kitto et al. 1997; Mayrsohn et al. 1978 as cited in NAS 1980; Mukund et al. 1996; NAS 1980; Wallace et al. 1987b). Ethylbenzene also is released from waste waters to the atmosphere in municipal sewer systems (Quigley and Corsi 1995). Therefore, the potential for human exposure to ethylbenezene is considerable. The medium most likely to be contaminated is air, although ethylbenzene has also

been detected in trace amounts in water supplies. Some ethylbenzene-containing wastes are designated as hazardous and are subject to EPA handling and recordkeeping requirements. Information regarding disposal practices would be useful in determining potential sources and levels of exposure to ethylbenzene.

According to the Emergency Planning and Community Right-to-Know Act of 1986,42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The TRI, which contains this information for 1994, became available in May of 1996. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Ethylbenzene is primarily partitioned to and transported in air (Dewulf and van Langenhove 1997; Eisenreich et al. 1981; Mackay 1979; Masten et al. 1994). The partitioning and transport processes in water, soil, and aquatic life are also well characterized (ASTER 1995; Dewulf et al. 1996; EPA 1980; Kawamura and Kaplan 1983; Ligocki et al. 1985; Swann et al. 1983). Transformation and degradation processes have also been well studied in air (Atkinson and Carter 1984; Atkinson et al. 1978; Grovenstein and Mosher 1970; Herron and Huie 1973; Hoshino et al. 1978; O'Brien et al. 1975; Ohta and Ohyama 1985; Ravishankara et al. 1978; Yanagihara et al. 1977), water (Acton and Barker 1992; Anid et al. 1993; Bouwer and McCarty 1984; Burback and Perry 1993; Ehrhardt and Petrick 1984; Gschwend et al. 1982; Hutchins 1991; Masten et al. 1994; Wakeham et al. 1983; Wilson et al. 1986), and in soil and sediment (Bestetto and Galli 1984 as cited in ECETOC 1986; Chen and Taylor 1995; Hutchins 1991; Hutchins et al. 1991; Jamison et al. 1970; Ramanand et al. 1995; Van der Linden and Thijsse 1965; Yadav and Reddy 1993; Zappi et al. 1996). Additional information on the kinetics of degradation, especially in the vicinity of hazardous waste sites, would be helpful in assessing the risk of exposure to individuals living or working near areas where ethylbenzene might persist in the soil.

Bioavailability from Environmental Media. Ethylbenzene is absorbed following inhalation, oral, and dermal exposures. Information is available on its absorption from air and water, but more data are needed on its oral and dermal bioavailability and absorption from soil and food. Under certain soil conditions, the chemical may persist for longer periods of time. Based on the moderate affinity of ethylbenzene for soil, especially soils with relatively high organic carbon content, individuals who work with or children who play in ethylbenzene-contaminated soil may be at risk of exposure via dermal contact or via consumption of contaminated soil from their unwashed hands. Because of the low bioconcentration factor (BCF) values calculated for ethylbenzene, food would not be expected to be significant sources of ethyl-

benzene exposure. More information on the conditions under which high concentrations of ethylbenzene may persist in soil long enough to become bioavailable through dermal contact with soil, ingestion of soil from unwashed hands, or from contaminated plant material would be useful in fully evaluating the risk posed by this compound at hazardous waste sites.

Food Chain Bioaccumulation. The available data indicate that ethylbenzene does not significantly bioaccumulate in aquatic or terrestrial food chains (BCF value = 167) (ASTER 1995; EPA 1989b; Nunes and Benville 1979) and is therefore unlikely to result in human exposure via ingestion of contaminated foods. However, little information on food residues in commercially important fish and shellfish species is currently available. Additional data on bioaccumulation would be helpful for several commercially important fish and shellfish species.

Exposure Levels in Environmental Media. An extensive amount of atmospheric monitoring data exists and much of it is current (Goldberg et al. 1995; Kostiainen 1994; Mukerjee et al. 1997; Quigley and Corsi 1995; Shah and Heyerdahl 1988; Wallace et al. 1987a, 1987c; Zielinska et al. 1996; Zweidinger et al. 1988). Ethylbenzene has also been detected in surface and groundwater (Barker 1987; Borden and Yanoschak 1990; Chen and Zoltek 1995; Cole et al. 1984; Cotruvo 1985; EPA 1985b; Gschwend et al. 1982; Krill and Sonzogni 1986; Quigley and Corsi 1995; Sauer et al. 1982; Staples et al. 1985; Stubin et al. 1996; Stuermer et al. 1982; Tester and Harker 1981), sediment (Staples et al. 1985), a limited number of foodstuffs (Ferrario et al. 1985; Gorna-Binkul et al. 1996; Kinlin et al. 1972; Lovegren et al. 1979; Nicola et al. 1987); and in cigarette smoke (Hodgson et al. 1996; Martin et al. 1997; Wallace 1986; Wallace et al. 1987c). Most of these data have been collected within the last 10 years. Additional data on the human intake of ethylbenzene from various contaminated environmental media would be helpful. More information on human intake from contaminated water (via dermal, inhalation, or oral exposures), foodstuffs, and soil or sediment (via oral and dermal exposures) would be useful in assessing the risk associated with these possible sources for individuals living near hazardous waste sites.

Reliable monitoring data for the levels of ethylbenzene in contaminated media at hazardous waste sites are needed so that the information obtained on levels of ethylbenzene in the environment can be used in combination with the known body burdens of ethylbenzene to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Ethylbenzene and its metabolites have been detected in human blood (Angerer and Wulf 1985), urine (Bardodejova 1970; Dutkiewicz and Tyras 1967; Engstrom and Bjurstrom 1978; Gromiec and Piotrowski 1984; Kiese and Lenk 1974; Sullivan et al. 1976; Yamasaki 1984), breast milk (Pellizzari et al. 1982), and adipose tissue (Engstrom and Bjurstrom 1978; Stanley 1986). Most of the monitoring data have come from occupational studies of specific worker populations exposed by inhalation. Members of the general population can be exposed to ethylbenzene through inhalation of fumes while pumping gas or riding in gasoline-powered vehicles (Backer et al. 1997; Lawryk and Weisel 1996; Lawryk et al. 1995). More information of general population exposure to ethylbenzene would be useful. Little information is available on the dietary intake of this chemical. Exposures from this route are likely to be low, except for the consumption of contaminated drinking water by populations living in the vicinity of hazardous waste sites, leaking underground storage tanks, or municipal landfills. More information on the dietary intake of ethylbenzene would be useful, given the possible importance of this exposure route for these populations.

While some information is available on absorption of ethylbenzene from aqueous solutions via dermal exposure (Dutkiewicz and Tyras 1967; Gromiec and Piotrowski 1984), additional information is needed to determine the bioavailability of ethylbenzene adsorbed to soil or sediment and its ultimate absorption via dermal contact or via ingestion of contaminated soils and sediments.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. No specific exposure studies on exposures of children were found. When the data need on soil bioavailability for oral and dermal exposure has been addressed, a better assessment can be made on whether soil pica and playing in dirt is a health risk issue for children. Ethylbenzene has been detected in breast milk samples collected from 8 or 12 women from various cities in the United States; however, the concentrations were not reported (Pellizzari et al. 1982). A study to determine current ethylbenzene residues and their sources in breast milk of members of the general population would be helpful.

Current information on whether children are different in their weight-adjusted intake of ethylbenzene via oral and dermal exposures was not located. A study to determine this information would be useful.

Exposure Registries. No exposure registries for ethylbenzene were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.8.2 Ongoing Studies

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, will be analyzing human blood samples for ethylbenzene and other volatile organic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

Information about other ongoing studies was obtained from a search of Federal Research in Progress (FEDRIP 1998). These studies are listed in Table 5-3.

Table 5-3. Ongoing Studies on Environmental Effects of Ethylbenzene

Investigator	Affiliation	Research description
Gibson DT	University of Iowa College of Medicine, Iowa City, IA	Mechanisms of enzymatic oxygen fixation
Lieberman RA	Physical Optics Corp., Torrance, CA	Optical sensing and signal identification for bioremediation process control
Logan BE, Arnold RG	Pennsylvania State University, Department of Civil and Environmental Engineering, University Park, PA	Biodegradation of subsurface pollutants by chlorate-respiring microorganisms
Nanny MA	University of Oklahoma, Department of Civil Engineering and Environmental Science, Norman, OK	Molecular-level characterization of bonding and bioavailability of monoaromatic pollutants associated with
Neidle E	University of Georgia Research Foundation, Athens, GA	Regulation of *Acinetobacter calcoaceticus* benzoate degradation
Smith MKL	Bend Research, Inc., Bend, OR	A membrane-based process for the removal of BTEX from glycol dehydration vents
Spormann AM	Stanford University, Department of Civil Engineering, Stanford, CA	Microbial degradation of aromatic hydrocarbons under anaerobic conditions
Starr RC	Idaho Falls, ID	Field demo oxygen for BTEX
Stuck JW	University of Illinois, Natural Resources and Environmental Sciences, Urbana, IL	Surface chemistry of oxidized and reduced clay minerals
Vroblesky DA	Department of the Interior, U.S. Geological Survey, Water Resources Division	Remediation of JP-4 contamination using hydraulic containment and *in situ* biodegradation at the Defense Fuel Supply Center, Charleston, SC
Weiss MEG	Membrane Technoloy and Research, Menlo Park, CA	Control of glycol dehydrator benzene, toluene, ethylbenzene, and xylene emissions

Source: FEDRIP 1998

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring ethylbenzene, its metabolites, and other biomarkers of exposure and effect to ethylbenzene. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

Ethylbenzene can be determined in biological fluids and tissues and breath using a variety of analytical methods. Representative methods are summarized in Table 6- 1. Most analytical methods for biological fluids and tissues use headspace gas chromatographic (GC) analysis. Breath samples are usually collected on adsorbent traps or in sampling bags or canisters, then analyzed by GC.

The headspace method involves equilibrium of volatile analytes such as ethylbenzene between a liquid or solid sample phase and the gaseous phase. The gaseous phase in then analyzed by GC. There are two main types of headspace methodology: static (equilibrium) headspace and dynamic headspace which is usually called the “purge-and-trap” method (Seto 1994). The static headspace technique is relatively simple, but may be less sensitive than the purge-and-trap method. The purge-and-trap method, while providing increased sensitivity, requires more complex instrumentation and may result in artifact formation (Seto 1994). Packed columns and capillary columns are used for chromatographic separation, followed by identification and quantitation using various detectors; flame ionization detection (FID) and mass spectrometry (MS) are used most often. Other sample preparation method have been used, but less frequently. Solvent extraction permits concentration, thereby increasing sensitivity, but the extraction solvent can interfere with analysis. Direct aqueous injection is a very rapid method, but sensitivity is low and matrix effects can be a serious problem.

Table 6-1. Analytical Methods for Determining Ethylbenzene in Biological Samples

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Whole blood	Purge and trap	cap. GC/MS	0.015–0.020 ppb	114–118	Ashley et al. 1992, 1994
Blood	Direct analysis via inertial spray extraction interface	GC/MS	<1 ppb	No data	St-Germain et al. 1995
Blood	Automated head space	cap. GC/FID	0.002 µg/mL	90–110 (estimated)	Otson and Kumarathasan 1995
Blood	Dynamic headspace	cap GC/FID	50 ng/L (calculated)	39	Fustinoni et al. 1996
Urine	Purge and trap	cap. GC/MS	No data	64–123 for model compounds	Michael et al. 1980
Urine	Dynamic headspace	cap. GC/FID	50 ng/L (calculated)	61	Fustinoni et al. 1996
Mother's milk	Purge and trap	cap. GC/MS	No data	35–88 for model compounds	Michael et al. 1980
Brain tissue (post mortem)	Modified headspace (full evaporation technique)	cap. GC-ITD	0.038 nmoles/sample	80–120	Schuberth 1996
Fat tissue	Add saline; freeze; thaw to 0 °C prior to analysis; add CS_2; inject into GC	GC/FID; conf. GC/MS	No data	No data	Wolff et al. 1977
Adipose tissue	Purge and trap	cap. GC/MS	No data	13–80 for halogenated hydrocarbons	Michael et al. 1980
Breath	Collection via spirometer into passivated canisters	cap. GC/MS	low µg/m^3 levels	77–82	Thomas et al. 1991
Breath	Collection via spirometer onto charcoal traps; microwave desorption	cap. GC/MS-SIM	0.2 µg/m^3 (1 L sampled)	No data	Riedel et al. 1996

cap. = capillary; conf. = confirmation; FID = flame ionization detector; GC = gas chromatography; HPLC = high performance liquid chromatography; ITD = ion trap detector; MS = mass spectrometry; SIM = selected ion monitoring

A spirometer is usually used for the collection of breath samples. The device is used to provide clean air for inhalation and a mechanism for pumping exhaled breath into the collection media (Pellizzari et al. 1985). The breath samples are collected into Tedlar bags with subsequent adsorption onto Tenax traps (Pellizzari et al. 198.5) or into passivated stainless steel canisters (Thomas et al. 1991). The Tenax traps are analyzed by thermal desorption GC techniques, and canister samples are analyzed by GC as well.

A sensitive and reliable method for identification and quantitation of ethylbenzene in samples of whole blood taken from humans following exposure to volatile organic compounds (VOC) has been developed by Ashley and coworkers at the Centers for Disease Control and Prevention (Ashley et al. 1992, 1994). The method involves purge-and-trap of a 10 mL blood sample with analysis by capillary GC/MS. Anti-foam procedures were used, as well as special efforts to remove background levels of VOCs from reagents and equipment (Ashley et al. 1992). The method is sensitive enough (ppt levels) to determine background levels of VOCs in the population and provides adequate accuracy (114-l 18% recovery) and precision (16-44% RSD) for monitoring ethylbenzene in the population.

Few methods are available for the determination of ethylbenzene in body fluids and tissues other than blood. A modified dynamic headspace method for urine, mother's milk, and adipose tissue has been reported (Michael et al. 1980). Volatiles swept from the sample are analyzed by capillary GC/FID. Acceptable recovery was reported for model compounds, but detection limits were not reported (Michael et al. 1980). Ethylbenzene in brain tissue may be determined using a headspace, capillary/ion trap detector (ITD) technique (Schuberth 1996). Recovery was good (80-120%) as was precision (≈20% RSD); the detection limit was reported as 4 ng/sample (0.038 nmoles) (Schuberth 1996).

Sensitive, reliable methods are available for measuring ethylbenzene in breath. Exhaled breath is collected using a spirometer. The exhaled breath is collected into Tedlar bags for later transfer to adsorption tubes (Wallace et al. 1982), into passivated canisters (Thomas et al. 1991), or directly onto adsorbent traps (Riedel et al. 1996). The spirometer system, using adsorption onto Tenax traps and analysis by thermal desorption/capillary GC/MS techniques, was field-tested over the course of a very large exposure study (Wallace 1987). The quantitation limit was = 1 $\mu g/m^3$, recovery was 91-100%, and the precision for duplicate samples was 130% RSD (Wallace 1987). Advances in the methodology include development of a more compact system with collection in 1.8 L canisters (Thomas et al. 1992). Recovery of ethylbenzene is 92-104%, precision for duplicate samples is <3% RSD, and the detection limit was estimated as 3 $\mu g/m^3$

for ethylbenzene (Thomas et al. 1992). Further modifications have resulted in a suitcase size breath sampling device (Raymer et al. 1994). Some testing has been conducted, but performance data are not available.

6.2 ENVIRONMENTAL SAMPLES

Methods are available for determining ethylbenzene in a variety of environmental matrices. A summary of representative methods is shown in Table 6-2. Validated methods, approved by agencies and organizations such as EPA, ASTM, APHA and NIOSH, are available for air, water, and solid waste matrices. Gas chromatography is the most widely used analytical technique for quantifying concentrations of ethylbenzene in environmental matrices. Various detection devices used for GC include the FID, MS, and the photoionization detector (PID). Because of the complexity of the sample matrix and the usually low concentrations of volatile organic compounds (VOCs) in environmental media, sample preconcentration is generally required prior to GC analysis. Air samples may be collected and concentrated on adsorbent or in canisters for subsequent analysis. Methods suitable for determining trace amounts of ethylbenzene in aqueous and other environmental media include three basic approaches to the pretreatment of the sample: gas purge-and-trap technique, headspace gas analysis, and extraction with organic solvent.

Gas purge-and-trap is the most widely used method for the isolation and concentration of VOCs in environmental samples (Lesage 1993). The purge-and-trap technique offers advantages over other techniques in that it allows facile isolation and concentration of target compounds, thereby improving overall limits of detection and recovery of sample. Detection limits of less than 1 μg of ethylbenzene per liter of sample have been achieved (APHA 1995c; EPA 1984c, 1991a, 1991e, 1992). A serious drawback of this technique, particularly for quantitative analysis, is interference by impurities found in the stripping gas (EPA 1994c).

A purge-and-trap method with GC/FID analysis (Otson and Williams 1982) or GC/MS (Otson and Chan 1987) has been reported for the analysis and quantitation of ethylbenzene in environmental samples. Detection limits of <0.1 μg/L for GC/FID analysis and 0.1 pg/L were reported. Accuracy was also good, 74-88% (Otson and Chan 1987; Otson and Williams 1982).

Table 6-2. Analytical Methods for Determining Ethylbenzene in Environmental Samples

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Occupational air	Collection on charcoal adsorbent tube; desorption with CS_2	GC/FID	0.001–0.01 mg/sample[a]	Bias -7.6%	NIOSH 1994 (NIOSH Method 1501)
Ambient air	Collection on Tenax adsorbent; thermal desorption	cap. GC/MS	20 ng estimated[a]	No data	EPA 1988e (Method TO-1)
Ambient air	Collection in passivated stainless steel canisters	cap. GC/MS or PID or FID	No data	No data	EPA 1988f (Method TO-14)
Ambient air	Collection on Tenax adsorbent; thermal desorption	cap. GC/MS	2 ng[a]	No data	Pellizzari et al. 1993 (IARC Method 6)
Ambient air	Collection in canisters	GC/MS	0.2 ppbv	bias -8.1%	McClenny and Fortune 1995 (CLP Method)
Ambient air	Collection on multisorbent traps; automated preconcentration	cap. GC/MS	0.036 ppbv	102	Oliver et al. 1996
Ambient air	Collection on multisorbent traps; thermal desorption with modified cryofocussing	cap. GC/FID	0.25 ppbv	98	Oliver et al. 1996
Indoor air	Collection on Tenax acsorbent; thermal desorption	GC/MS	0.05–0.2 µg/m^3	No data	Kostianinen 1994
In-vehicle air	Collection on Tenax or multisorbent traps; thermal desorption	cap. GC/MS-SIM	No data	No data	Lawryk and Weisel 1996
Flue gas	Collection on adsorbent traps using probe; thermal desorption	cap. GC/FID	0.05 µg/m^3 (est.)	No data	Jay and Stieglitz 1995
Product emissions	Collection on charcoal traps; desorption with CS_2	cap. GC/FID	No data	No data	Wadden et al. 1995
Tobacco smoke	Collection on multisorbent traps; thermal desorption	PLOT col. GC/MS	No data	No data	Barrefors and Petersson 1993

Table 6-2. Analytical Methods for Determining Ethylbenzene in Environmental Samples (continued)

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water	purge and trap	GC/PID	0.01–0.04 µg/L	98–101	EPA 1991d (EPA Method 502.2)
Drinking water	purge and trap	GC/PID; conf. on second column or GC/MS	0.002 µg/L	93	EPA 1991e (EPA Method 503.1)
Drinking water	purge and trap	GC/MS	1–2 µg/L	No data	EPA 1991f (EPA Method 524.1)
Drinking water	purge and trap	cap. GC/MS	0.06 µg/L	96–99	EPA 1992 (EPA Method 524.2)
Drinking water	purge and trap	GC/FID or GC/MS	low µg/L	84–114	ASTM 1994a (ASTM Method D 3871)
Drinking water	direct injection	GC/FID	~1 mg/L	No data	ASTM 1994b (ASTM Method D 2908)
Wastewater	purge and trap	GC/PID; conf. on second column	0.2 µg/L	98	EPA 1984c (EPA Method 602)
Wastewater	purge and trap	GC/MS	7.2 µg/L	100–103	EPA 1984d (EPA Method 624)
Water	closed-loop stripping	cap. GC/MS	50 ng/L (instrumental)	No data	APHA 1995a (Method 6040B)
Wastewater	purge and trap	GC/MS	7.2 µg/L		APHA 1995b (Method 6210B)
Wastewater	purge and trap	GC/PID; conf. on second column or GC/MS	0.2 µg/L	93	APHA 1995c (Method 6220B)
Wastewater	purge and trap	GC/PID	0.01–0.05 µg/L	93	APHA 1995d (Method 6220C)
Solid waste	direct injection or purge and trap	cap. GC/PID	~1 µg/L (soil, sediment); ~0.1 mg/kg (wastes)	101	EPA 1994d (SW846 Method 8021A)
Solid waste	purge and trap	cap. GC/PID	~1 µg/L (soil, sediment); ~0.1 mg/kg (wastes)	101	EPA 1995a (SW846 Method 8021B, proposed)

Table 6-2. Analytical Methods for Determining Ethylbenzene in Environmental Samples (continued)

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Solid waste	purge and trap	cap. GC/MS	~5 µg/kg (soil, sediment)	99	EPA 1994e (SW846 Method 8260A)
Solid waste	various options including purge and trap, headspace, closed system vacuum distillation	cap. GC/MS	purge and trap: ~5 µg/kg (soil and sediment); ~ 0.5 mg/kg (wastes)	90–112 (purge and trap)	EPA 1995b (SW846 Method 8260B, proposed)
Plant foliage	Solvent extraction; filtration	cap. GC/SM-SIM	50 pg/µL extract	No data	Keymuelen et al. 1991
Fish	Solvent extraction; cleanup on florisil column; solvent microextraction	GC/FID	5 µg/g[b]	98–102	Karasek et al. 1987
Fish and sediment	Homogenization; freezing and vacuum extraction	cap. GC/MS	25 ppb[b]	Sediments, 97 recovery; fish, 76% average for all analytes	Hiatt 1981, 1983
Eggs	head space	cap. GC/PID; conf. by GC/MS	0.002 µg/mL	94 (white); 49 (whole); 21 (yolk)	Stein and Narang 1990
Fruits and vegetables	Solvent extraction; filtration	cap. GC/MS-SIM	No data	No data	Górna-Binkul et al. 1996
Olives and olive oil	Headspace	cap. GC/MS	Low µg/kg levels	No data	Biedermann et al. 1995
Cooked meat	Azeotropic distillation using Kilens-Nickerson estractor	cap. GC/MS	6 µg/kg	No data	Gramshaw and Vandenburg 1995
Food containers (polystyrene)	incubation with DMF; headspace	cap. GC/FID; conf. GC/MS	10 ppm	96–102	Sugita et al. 1995

[a] Sample detection limit will depend upon volume sampled. Value is estimated instrumental detection limit.
[b] Method detection limits were not provided; estimates cited are based on lowest concentrations used for method performance evaluation.

cap. = capillary; conf. = confirmation; CS_2 = carbon disulfide; DMF = dimethylformamide; FID = flame ionization detector; GC = gas chromatography; MeOH = methanol; MS = mass spectrometry; PID = photoionization detector; SIM = selected ion monitoring; UV = ultraviolet spectrophotometry

Extraction with organic solvents (liquid-liquid extraction) provides a simple, rapid screening method for semi-quantitative determination of ethylbenzene in aqueous samples containing limited number of VOCs, but is less effective for aqueous samples containing large numbers of VOCs. Furthermore, interference from the organic extraction solvent (hexane) makes it more difficult to completely identify all components (Karasek et al. 1987; Otson and Williams 1981).

Ethylbenzene may be determined in occupational air using collection on multisorbent cartridges, solvent desorption and analysis by GC/FID (NIOSH 1994). Accuracy is very good (-7.6% bias); detection limits depend upon the amount of air sampled. Ambient air samples may also be collected on adsorbent traps (EPA 1988e; Pellizzari et al. 1993) or in stainless steel canisters (EPA 1988f; McClenny and Fortune 1995). Recovery for Tenax traps is very good, ranging from 91 to 100% (Wallace 1987). Little information on accuracy is available for multisorbent traps, but good recovery (102%) has been reported (Oliver et al. 1996a). Bias of -8.1% for canister collection has been reported (McClenny and Fortune 1995). Detection limits depend upon the amount of air sampled, but values in the sub-ppb range have been reported (Kostiainen 1994; McClenny and Fortune 1995; Oliver et al. 1996a, 1996b).

Purge-and-trap methodology is used most often for determination of ethylbenzene in water and hazardous wastes (Lesage 1993). The method was developed by Bellar and Lichtenberg (1974) for waste water. An inert gas is bubbled through the sample to strip out volatile components. The analytes in the gas stream are adsorbed onto sorbent traps, then thermally desorbed into the GC column. Very low detection limits for drinking water are reported for the purge-and-trap method with GC/PID (0.002-0.04 μg/L) (EPA 1991a, 1991e). Accuracy is very good (93-101% recovery) (EPA 1991a, 1991e). While the method is quite selective; confirmation using a second GC column or GC/MS is recommended (EPA 1991e). A sensitive (0.06 μg/L) and reliable method (96-99% recovery; <10% RSD) for drinking water uses capillary column GC/MS (EPA 1992a). Purge-and-trap methodology with analysis by GC/PID or GC/MS is used for waste waters (APHA 1995b, 1995c, 1995d; EPA 1984c, 1984d). The detection limits are lower for GC/PID (0.2.μg/L) (EPA 1984c) than for GC/MS (7.2 μg/L) (EPA 1984b), but confirmation on a second column is recommended (EPA 1984c) when PID is used. Recovery and precision are very good (98-103% recovery; < 10% RSD) (EPA 1984c, 1984d).

Soil, sediment, and solid waste samples are difficult to analyze. Volatilization during sample handling and homogenization can result in ethylbenzene losses. The wet sample is usually dispersed in a solvent, then

added to water for purge-and-trap/GC analysis (EPA 1994c). Capillary GC/PID or GC/MS analysis provides detection limits in the low ppb range for soil and sediment and in the sub-ppm range for solid wastes (EPA 1994d, 1994e, 1995a, 1995b).

Few methods are available for the determination of ethylbenzene in fish and biota. A method for the determination of ethylbenzene in fish at low ppm levels using solvent extraction with GC/FID analysis has been reported (Karasek et al. 1987). A procedure to identify and quantify ethylbenzene in fish samples by vacuum distillation with capillary column GC/MS has been reported (Hiatt 1981, 1983). Recovery of 98-102% from spiked fish tissue was reported, but detection limits were not reported (Hiatt 1981). Purgeand-trap/capillary GC/MS has also been used for the determination of ethylbenzene in fish. Performance data for fish tissue samples were not reported (Dreisch and Munson 1983).

Few methods are available for the determination of ethylbenzene in food. Available methods involve solvent extraction (Goma-Binkul et al. 1996), headspace purge (Biedermann et al. 1995), and azeotropic distillation (Gramshaw and Vandenburg 1995) followed by capillary GC/MS or GC/PID analysis. Detection limits are in the low pg/kg range (Biederman et al. 1995; Gramshaw and Vandenburg 1995). Little performance data are available. Recoveries of 21% (egg yolk) to 94% (egg white) were reported for headspace/capillary GC/PID analysis of eggs (Stein and Narang 1990).

Screening methods and field-portable methods may be useful analytical tools. Soil screening for petroleum hydrocarbons, including ethylbenzene, can be conducted using immunoassay procedures. Sensitivity is in the ppm range (EPA 1995c). Solid phase microextraction (SPME) has been tested as a screening method for water (Shirey 1995). The method is used in conjunction with capillary GC techniques. Portable GCs have been used for field monitoring of air (Berkley et al. 1991), water (Driscoll and Atwood 1993), soil (Driscoll and Atwood 1993), and hazardous waste (Overton et al. 1995). There are several studies which compare portable GC methods with laboratory methods (Berkley et al. 1991; Driscoll and Atwood 1993). A thorough discussion of the strengths and problems of portable GC methods is available (Berkley et al. 1996).

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of ethylbenzene is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of ethylbenzene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Exposure to ethylbenzene can be determined by the detection of mandelic acid and phenylglycolic acid in urine or by direct detection of ethylbenzene in human blood. Environmental exposures to ethylbenzene can result in detectable levels in human tissues. Existing methods for the determination of ethylbenzene in blood have the sensitivity necessary (0.008-0.012 ppb) (Ashley et al. 1992) to detect and measure low to trace levels of ethylbenzene in blood that might be present in the general population, as well as concentrations of ethylbenzene that might be associated with specific health effects. Methods for measurement of ethylbenzene in exhaled breath are sensitive enough (low $\mu g/m^3$) (Thomas et al. 1991) to provide background levels of ethylbenzene in the general population as well as to measure exposure. Additional performance information would be helpful, as would further development of a portable breath collection system. Information on levels of ethylbenzene in tissues is limited and the existing methods are not as well characterized. Improvements in the sensitivity of the methods for measuring concentrations of ethylbenzene in tissues and additional performance data would be helpful.

Methods for measuring metabolites and biomarkers for ethylbenzene are shown in Table 6-3. Methods exist for measuring ppm levels of ethylbenzene metabolites in urine (Ogata and Taguchi 1987, 1988; Sollenberg et al. 1985). They are sufficiently sensitive for measuring occupational exposure to ethylbenzene. These analytical methods are reliable and precise, but may not be sensitive enough to measure non-occupational exposure. Improvements in the sensitivity of the methods for measuring concentrations of ethylbenzene in tissues, and improvements in the sensitivity for measurement of metabolites in urine would allow better assessment of the correlation between levels in these media and observed health effects.

No specific biomarkers of effect for ethylbenzene were identified.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Sensitive methods are available for measuring background levels of ethylbenzene in air, water, and wastes, the media of most concern for exposure of the general population and those populations located near hazardous waste sites. Few methods are available for measuring levels of ethylbenzene in fish, plants and biota. Detection limits in the low ppb range have been reported (Dreisch and Munson 1983; Hiatt 198 1; Karasek et al. 1987; Keymuelen et al. 1991), but other performance data are generally lacking. Few methods are available for measuring levels of ethylbenzene in food. Little performance data are available for the available methods. Although several good analytical methods are available for detecting ethylbenzene in some environmental media, validated, reliable methods for measuring ethylbenzene in fish and foods are needed. These would be helpful in evaluating the potential for human exposure and health effects that might result from ethylbenzene contamination.

Methods for detecting environmental degradation products of ethylbenzene in environmental media are summarized in Table 6-4. Although methods are available for detecting major environmental degradation products (1-phenylethanol, acetophenone, benzaldehyde, for example) in reaction mixtures, it is not known whether these methods have the sensitivity and specificity for application to environmental media. Sensitive, reliable methods for determining degradation products in air, water, and waste would be helpful.

Table 6-3. Analytical Methods for Determining Biomarkers of Ethylbenzene in Biological Materials

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Accuracy % recovery	Reference
Urine (MA)	Dilution; centrifugation	HPLC/UV	MA 5 ng injected	MA 100–102	Ogata and Taguchi 1988
Urine (MA and PGA)	MeOH addition; centrifugation	HPLC	PGA $8.5x10^3$ µg/L MA $10x10^3$ µg/L	PGA 101 MA 102.6	Ogata and Taguchi 1987
Urine (MA and PGA)	Filtration; solvent extraction; evaporation and dissolution	HPLC/UV	MA, PGA $1.5x10^3$ µg/L	No data	Sollenberg et al. 1985
Urine (MA and PGA)	Filtration; solvent extraction; evaporation and dissolution	ITP	MA $6.1x10^3$ µg/L PGA $3.0x10^3$ µg/L	No data	Sollenberg et al. 1985

HPLC = high performance liquid chromatography; ITP = isotachophoresis; MA = mandelic acid; PGA = phenylglyoxylic acid; UV = ultraviolet (detection)

Table 6-4. Analytical Methods for Determining Environmental Degradation Products of Ethylbenzene

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Accuracy % recovery	Reference
Reaction mixtures	Solvent extraction; concentration	cap. GC/FID	No data	No data	Ehrhardt and Petrick 1984
Reaction mixtures	Centrifugation; solvent extraction; concentration	GC/FID; conf. GC/MS	No data	No data	Fukuda et al. 1989

FID = flame ionization detector; GC = gas chromatography; MS = mass spectrometry

6.3.2 Ongoing Studies

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing methods for the analysis of ethylbenzene and other volatile organic compounds in blood. These methods use purge-and-trap methodology, high resolution gas chromatography, and magnetic sector mass spectrometry which gives detection limits in the low parts per trillion (ppt) range.

EPA has initiated a program to identify or develop methods that can be used to measure chemical pollutants in dietary samples collected from individuals. Dr. Linda Sheldon at the Research Triangle Institute is evaluating methods for VOCs, including ethylbenzene, in composite food as a part of this program.

The EPA is conducting a pilot program for comprehensive monitoring of human exposure. The National Human Exposure Assessment Study (NHEXAS) is being conducted in three regions of the United States in order to establish relationships between environmental concentrations, exposure, dose, and health response and to determine the incidence and causes of high exposures, especially for biologically susceptible persons. One of the aims of the pilot study is to test measurement methodology for a variety of pollutants, including ethylbenzene, in air and water. As an adjunct to this pilot study, the EPA and the State of Minnesota are conducting a study of children’s exposure to toxic chemicals, including ethylbenzene.

7. REGULATIONS AND ADVISORIES

The national and state regulations and guidelines pertaining to ethylbenzene in air, water, and other media are summarized in Table 7- 1. No international regulations or guidelines applicable to ethylbenzene were found.

ATSDR has derived an intermediate inhalation minimal risk level (MRL) of 1.0 ppm for ethylbenzene based on a NOAEL of 97 ppm for developmental effects in Wistar rats (Andrew et al. 1981).

The EPA oral reference dose (RfD) for ethylbenzene is 0.1 mg/kg/day, based on the LOAEL for liver and kidney toxicity in rats administered 291 mg/kg/day ethylbenzene (IRIS 1996). The EPA inhalation reference concentration (RfC) for ethylbenzene is 1 mg/m^3 based on developmental toxicity seen in rats and rabbits exposed to 4,340 mg/m^3 (IRIS 1996).

The EPA has classified ethylbenzene as Group D (not classifiable as to human carcinogenicity), due to the lack of animal bioassays and human studies (IRIS 1996). The International Agency for Research on Cancer (IARC) and the National Toxicology Program have not classified the chemical for carcinogenicity.

Ethylbenzene is on the list of chemicals subject to the requirements of "The Emergency Planning and Community Right-to-Know Act of 1986" (EPCRA) (EPA 1988a). Section 3 13 of Title III of EPCRA, requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media (U.S. Congress 1986).

OSHA requires employers of workers who are occupationally exposed to ethylbenzene to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs). The employer must use controls and practices, if feasible, to reduce exposure to or below an 8-hour time-weighted average (TWA) of 100 ppm (OSHA 1974).

The EPA regulates ethylbenzene under the Clean Air Act (CAA) and has designated ethylbenzene as a hazardous air pollutant (HAP). The major source category for which ethylbenzene emissions are controlled

is the synthetic organic chemicals manufacturing industry (SOCMI)-equipment leaks (EPA 1983a), distillation operations (EPA 1990), and reactor processes (EPA 1993a).

Ethylbenzene is regulated by the Clean Water Effluent Guidelines in Subchapter N of Title 40 of the Code of Federal Regulations. Electroplating is the point source category for which ethylbenzene is controlled as a total toxic organic (EPA 198 la). The point source categories for which ethylbenzene has a specific regulatory limitation include organic chemicals, plastics, and synthetic fibers (EPA 1987a, 1987b, 1987d, 1987e, 1987f, 1987g,1987h, 19871).

The Resource Conservation and Recovery Act (RCRA) identifies ethylbenzene as a hazardous waste from non-specific sources and has assigned the hazardous waste number, F003 (EPA 1981c).

Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), owners of vessels or facilities are required to immediately report release of ethylbenzene equal to or greater than the reportable quantity of 1,000 pounds (454 kg) (EPA 1985b).

Table 7-1. Regulations and Guidelines Applicable to Ethylbenzene

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
WHO	Drinking-water guideline values for *health-related organics*	300µg/L	WHO 1996
NATIONAL			
Regulations: a. Air:			
OSHA	Air contaminants		
	Permissible Exposure Limit (PEL) 8-hr. Time weighted average (TWA)	100 ppm	29 CFR 1910.1000 OSHA 1974[a]
EPA OAR	Hazardous Air Pollutants	Yes	Clean Air Act Amendment Title III, Section 112 (b) U.S. Congress 1990
	Standards of Performance for New Stationary Sources-		
	Subpart VV: Equipment leaks of VOCs in the Synthetic Organic Chemicals Manufacturing Industry (SOCMI)--chemicals produced by affected facilities	Yes	40 CFR 60.489 EPA 1983a
	Subpart NNN: VOC emissions from SOCMI distillation operations--chemical affected	Yes	40 CFR 60.667 EPA 1990
	Subpart RRR: VOC emissions from SOCMI reactor processes--chemicals affected	Yes	40 CFR 60.707 EPA 1993a
	National Emission Standards for Hazardous Air Pollutants for Source Categories		
	National Emission Standards for Organic Hazardous Air Pollution from the Synthetic Organic Chemical Manufacturing Industry-Delegation of Authority	Yes	40 CFR 63.106 EPA 1994a
	Regulation of Fuels and Fuel Additives Reformulated Gasoline-Measurement of reformulated gasoline fuel parameters	Yes	40 CFR 80.46 EPA 1994c
b. Water			
EPA ODW	National Revised Primary Drinking Water Regulations: Maximum Contaminant Levels-		
	Maximum contaminant levels for organic chemicals	0.7 mg/L	40 CFR 141.61 EPA 1991a
	BAT for organic contaminants listed in 40 CFR 141.61 (a) and (g)	GAC PTA	

Table 7-1. Regulations and Guidelines Applicable to Ethylbenzene (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
EPA OW			
	Designation of Hazardous Substances		
	List of hazardous substances	Yes	40 CFR 116.4 EPA 1978
	Determination of Reportable Quantities for Hazardous Substances		
	RQ of hazardous substances designated pursuant to Section 311 of the CWA	1000 pounds (454 kg)	40 CFR 117.3 EPA 1985d
	EPA Administered Permit Programs: The NPDES-		
	Organic toxic pollutants in each of four fractions in analysis by GC/MS	Yes	40 CFR 122, App. D EPA 1983b
	Criteria and Standards for the NPDES-		
	Instructions for Form 2C, application for permit to discharge wastewater--hazardous substances	Yes	40 CFR 125 EPA 1984a
	Methods for organic chemical analysis of municipal and industrial wastewater (Methods 602, 624, and 1624)	Yes	40 CFR 136, App. A EPA 1973
	Designated as a toxic pollutant under Section 307 (a)(1) of the Federal Water Pollution Control Act	Yes	40 CFR 401.15 EPA 1979
	General pretreatment regulations for existing and new sources of pollution-		
	List of toxic pollutants	Yes	40 CFR 403, App. B EPA 1986a
	Pollutants eligible for a removal credit	Yes	40 CFR 403, App. G EPA 1993b
	Electroplating Point Source Category-		
	General definition	Yes	40 CFR 413.02 EPA 1981a
	Organic Chemicals, Plastics, and Synthetic fibers		
	Subpart B-Rayon Fibers-PSES Maximum for any one day Maximum for monthly average	 380 µg/L 142 µg/L	40 CFR 414.25 EPA 1987a
	Subpart C-Other Fibers-PSES Maximum for any one day Maximum for monthly average	 380 µg/L 142 µg/L	40 CFR 414.35 EPA 1987b

Table 7-1. Regulations and Guidelines Applicable to Ethylbenzene (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Subpart D-Thermoplastic Resins-PSES		40 CFR 414.45 EPA 1987d
	Maximum for any one day	380 µg/L	
	Maximum for monthly average	142 µg/L	
	Subpart E-Thermosetting Resins		40 CFR 414.55
	Maximum for any one day	380 µg/L	EPA 1987e
	Maximum for monthly average	142 µg/L	
	Subpart F-Commodity Organic Chemicals		40 CFR 414.65 EPA 1987f
	Maximum for any one day	380 µg/L	
	Maximum for monthly average	142 µg/L	
	Subpart G-Bulk Organic Chemicals-PSES		40 CFR 414.75 EPA 1987g
	Maximum for any one day	380 µg/L	
	Maximum for monthly average	142 µg/L	
	Subpart H-Speciality Organic Chemicals--		
	PSES		
	Maximum for any one day	380 µg/L	40 CFR 414.85
	Maximum for monthly average	142 µg/L	EPA 1987h
	Subpart J-Direct Discharge Point Source That Do Not Use End-of Pipe Biological Treatment-effluent limitations: BAT and NSPS		40 CFR 414.101 EPA 1987i
	Maximum for any one day	380 µg/L	
	Maximum for monthly average	142 µg/L	
	Steam Electric Power Generating *Point Source Category*		
	Pretreatment standards for new sources (PSNS)		40 CFR 423.17 EPA 1982a
	Maximum for any time	0.2 mg/L	
	List of 126 priority pollutants	Yes	40 CFR 423, App. A EPA 1982b
	Metal Finishing Point Source Category		
	Metal finishing subcategory-Definition of total toxic organics (TTO)	>0.01 mg/L	40 CFR 433.10 EPA 1983c
	Pesticide Chemicals		
	Subpart D-Test Methods for Pesticide Pollutants		40 CFR 455.50, Table 4 EPA 1993c
	BAT and NSPS effluent limitations for priority pollutants for direct discharge point sources that use end-of-pipe biological treatment		
	Daily maximum	108 µg/L	
	Monthly average	32 µg/L	

Table 7-1. Regulations and Guidelines Applicable to Ethylbenzene (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	BAT and NSPS effluent limitations for priority pollutants for direct discharge point sources that do not use end-of-pipe biological treatment		40 CFR 455.50, Table 5 EPA 1993c
	Daily maximum	380 µ/L	
	Monthly average	142 µg/L	
	PSES and PSNS for priority pollutants		40 CFR 455.50, Table 6 EPA 1993c
	Daily maximum	380 µ/L	
	Monthly average	142 µg/L	
EPA OWRS	Ambient Water Quality Criteria For the Protection of Human Health:		IRIS 1996
	Ingestion of water and aquatic organisms	1.4 mg/L	
	Ingestion of aquatic organisms only	3.28 mg/L	
c. Other:			
DOT	Hazardous Materials Table	UN 1975	49 CFR 172.101 DOT 1990a
	Hazardous substances other than radionuclides: RQ	1000 pounds (454 kg)	49 CFR 172.101, App. A DOT 1990b
EPA-OERR	List of Hazardous Substances and Reportable Quantities	1000 pounds (453.6 Kg) (statutory)	40 CFR 302.4 EPA 1985b
		1000 pounds (454 Kg) (final RQ)	
	Toxic Chemical Release Reporting: Community Right-to-know		
	Specific toxic Chemical Listings	Yes	40 CFR 372.65 EPA 1988a
EPA-OSW	Criteria for Municipal Solid Waste Landfills		
	Constituents for detection monitoring	Yes	40 CFR 258, App. I EPA 1991b
	List of hazardous inorganic and organic constituents	Yes	40 CFR 258, App. II EPA 1991c
	Lists of Hazardous Wastes		
	Hazardous wastes from non-specific sources- F003 wastes	Yes	40 CFR 261.31 EPA 1981c
	Standards for Owners and Operators of Hazardous Waste Treatment, Storage, and Disposal Facilities		
	Ground-water monitoring list	Yes	40 CFR 264, App. IX EPA 1987c

Table 7-1. Regulations and Guidelines Applicable to Ethylbenzene (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Land Disposal Restrictions-		
	Waste prohibitions-solvent wastes	Yes	40 CFR 268.30 EPA 1988b
	Treatment standards-applicability of treatment standards	Yes	40 CFR 268.40 EPA 1987j
	Treatment standards expressed as concentration in waste extract (technical amendment to final rule-40 CFR 268.40)	Wastewater 0.057 mg/L Nonwastewater 10 mg/kg	62 FR 7502 EPA 1997
	Universal treatment standards (technical amendment to final rule-40 CFR 268.40)	Wastewater 0.057 mg/L Nonwastewater 10 mg/kg	62 FR 7502 EPA 1997
EPA OPPTS	Chemical Information Rules		
	Chemical lists and reporting periods	Yes	40 CFR 712.30 EPA 1982c
	Health and Safety Data Reporting		
	Affected substances and mixtures	Yes	40 CFR 716.120 EPA 1988d
Guidelines:			
a: Air:			
ACGIH	Ceiling Limit for Occupation Exposure (TLV-STEL)	0.4 ppm (0.37 mg/m^3)	ACGIH 1996
	Biological Exposure Indices (BEI) Mandelic acid in urine ethyl benzene in end-exhaled air	 1.5 g/g creatinine	
NIOSH	Recommended Exposure Limit for Occupation Exposure--Time-weighted average (TWA)-up to 10 hours per 40-hour workweek	100 ppm (435 mg/m^3)	NIOSH 1997
	Recommended Exposure Limit for Occupation Exposure --Short-term exposure limit (STEL; 15-minute TWA	125 ppm (545 mg/m^3)	
b. Water:			
EPA ODW	1-d Health Advisory (child)-draft	20 mg/L	EPA 1995c
	10-d Health Advisory (child)-draft	3 mg/L	
	Lifetime Health Advisory (adult)-draft	0.7 mg/L	
	Longer-term Health Advisory-draft	1 mg/L (child) 3 mg/L (adult)	
	RfD	0.1 mg/kg/d	
	Maximum contaminant level goals (MCLGs) for organic contaminants	0.7 mg/L	40 CFR 141.50 EPA 1985a

Table 7-1. Regulations and Guidelines Applicable to Ethylbenzene (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
d. Other:			
ACGIH	Chemical Substance and other Issues Under Study	Yes	ACGIH 1996
EPA	Cancer Classification	D[a]	EPA 1995c
STATE			
Regulations and Guidelines:			
a. Air:	Average Acceptable Ambient Air Concentrations		NATICH 1992
AZ	1 hour	$4.5x10^{+3}$ µg/m^3 (1.036 ppm)	
	24 hours	$3.5x10^{+3}$ µg/m^3 (0.806 ppm)	
CT	8 hours	$8.70x10^{+3}$ µg/m^3 (2.004 ppm)	
FL-FtLdle	8 hours	4.40 mg/m^3 (1.013 ppm)	
FL-Pinella	8 hours	$4.35 x10^{+3}$ µg/m^3 (1.002 ppm)	
	24 hours	$1.04 x10^{+3}$ µg/m^3 (0.240 ppm)	
FL-Tampa	8 hours	4.35 mg/m^3 (1.002 ppm)	
LA	8 hours	$1.03x10^{+4}$ µg/m^3 (2.372 ppm)	
MA	24 hours	$1.8x10^{+2}$ µg/m^3 (0.041 ppm)	
	Annual	$1.8x10^{+2}$ µg/m^3 (0.041 ppm)	
ME	15 minutes	$5.4x10^{+4}$ µg/m^3 (12.437 ppm)	
	24 hours	$3.5x10^{+3}$ µg/m^3 (0.806 ppm)	
	1 year	$3.5x10^{+2}$ µg/m^3 (0.081 ppm)	
ND	1 hour	5.43 mg/m^3 (1.251 ppm)	
	8 hours	4.34 mg/m^3 (1.000 ppm)	
NV	8 hours	$1.04x10^{+1}$mg/m^3 (2.395 ppm)	
NY	1 year	$1.45x10^{+3}$ µg/m^3 (0.334 ppm)	

Table 7-1. Regulations and Guidelines Applicable to Ethylbenzene (continued)

Agency	Description	Information	References
STATE (cont.)			
OK	24 hours	$4.34x10^{+4}$ µg/m³ (9.996 ppm)	
SC	24 hours	$4.35x10^{+3}$ µg/m³ (1.002 ppm)	
TX	30 minutes	$2.0x10^{+3}$ µg/m³ (0.461 ppm)	
	Annual	$4.34x10^{+2}$ µg/m³ (0.100 ppm)	
VA	24 hours	$7.20x10^{+3}$ µg/m³ (1.658 ppm)	
VT	8 hours	$4.35x10^{+4}$ µg/m³ (10.019 ppm)	
WA-SWEST	24 hours	$1.45x10^{+3}$ µg/m³ (1.002 ppm)	
b. Water			
	Water Quality Criteria: Human Health		
AZ	Drinking water (guideline)	680 µg/L	FSTRAC 1995
CA	Drinking water (standard)	680 µg/L	
IL	Drinking water (guideline)	1 µg/L	FSTRAC 1990
KS	Drinking water (guideline)	680 µg/L	
MA	Drinking water (guideline)	700 µg/L	
	Groundwater (standard)	486 µg/L	MDEQE 1989
ME	Drinking water (guideline)	700 µg/L	FSTRAC 1995
MN	Drinking water (guideline)	700 µg/L	
NH	Drinking water (guideline)	700 µg/L	FSTRAC 1990
RI	Drinking water (guideline)	680 µg/L	
VT	Drinking water (standard)	680 µg/L	
WI	Drinking water (guideline)	700 µg/L	FSTRAC 1995

[a] A U.S. Court of Appeals rescinded the 1989 PELs promulgated by OSHA. Only PELs in place prior to the 1989 rule are currently allowed.
[b] The determinant is non-specific, since it is observed after exposure to some other chemicals.

BAT = Best Available Technology Economically Achievable; BEI = Biological Exposure CWA = Clean Water Act; EPA = Environmental Protection Agency; FSTRAC = Federal State Toxicology and Regulatory Alliance committee; GC/MS = Gas Chromatography/Mass Spectroscopy; IARC = International Agency for Research on Cancer; INCIN = Incineration; MCL = Maximum contaminant Level; MCLG = Maximum Contaminant Level Goal; NIOSH = National Institute of Occupational Safety and Health; NPDES = National Pollution Discharge Elimination System; NSPS = New Source Performance Standards; OAR - Office of Air and Radiation; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; PTA = Packed Tower Aeration; PEL = Permissible Exposure Limit; PSES = Pretreatment Standards for Existing Sources; RfD = Reference Dose; RQ = Reportable Quantities; SOCMI = Synthetic Organic Chemicals Manufacturing Industry; STEL = Short-term exposure Limit; TLV = Threshold Limit Value; TWA = Time-weighted Average; VOC = Volatile Organic Compound; WHO = World Health Organization

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9. GLOSSARY

Absorption-The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure--Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption-The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc}) The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)-The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)-is usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model-is a statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)-The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers-are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)-The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen-A chemical capable of inducing cancer.

Case-Control Study-A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report-describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series-describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value-A concentration of a substance that should not be exceeded, even instantaneously. Chronk Exposure-Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study-A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study-A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs-substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity-The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship--the quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity-Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory-An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology-refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity-a specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life-a measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)-The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence-The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure-Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunological Effects-are functional changes in the immune response.

Immunologic Toxicity-The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro-Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo-Occurring within the living organism.

Lethal Concentration$_{(10)}$(LC$_{LO}$)-The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$(LC$_{50}$) A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(10)}$(LD$_{LO}$)-The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$(LD$_{50}$)-The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$(LT$_{50}$)-A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)-The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects-represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations-Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL) -An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF) A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity-State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality-Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen-A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy-The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.
Neurotoxicity-The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)-The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})-The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio-a means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound- a phosphorus containing organic compound and especially a pesticide that acts by inhibiting choline&erase.

Permissible Exposure Limit (PEL)-An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an &hour shift of a 40 hour workweek.

Pesticide--general classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics-is the science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model-is a set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model-is a type of physiologically-based doseresponse model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model-is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information 4such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence-The number of cases of a disease or condition in a population at one point in time.

Prospective Study-A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Recommended Exposure Limit (REL)-A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)-An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)-An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the No-Observed-Adverse-Effect Level (NOAEL- from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)-The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity-The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study-A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to casual factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk-the possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor-An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio-The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)-The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 rnin continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Target Organ Toxicity-This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratoge-A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)-An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)-An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$(TD$_{50}$)-A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic-The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)--A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using Lowest-Observed-Adverse-Effect Level (LOAEL) data rather than No-Observed-Adverse-Effect Level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic-any chemical that is foreign to the biological system.

APPENDIX A

ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEETS

Chemical name(s): Ethylbenzene
CAS number(s): 100-41-4
Date: May 1999
Profile status: Second Draft
Route: [X] Inhalation [ ] Oral
Duration: [] Acute [X] Intermediate [ ] Chronic
Key to figure: 55
Species: rat

MRL: 1.0 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Andrew et al. 1981

Experimental design: Andrew et al. (1981) investigated the teratologic effects of ethylbenzene and 2-ethoxyethanol exposures to rats. Wistar rats were exposed to 0, 100, or 1,000 ppm (average exposure chamber concentration measured at 0, 97±6, or 959±88 ppm, respectively) ethylbenzene for 7 hours a day, 5 days a week for 3 weeks. They were then mated and exposed to 0, 100, or 1,000 ppm (average exposure chamber concentration measured at 96±7 or 985±62 ppm, respectively) ethylbenzene 7 hours a day, 5 days a week through gestational day (Gd) 19. The rats were then killed and examined at Gd 21. Based on various combinations of pre-gestational and gestational exposures, 6 exposure groups were formed as follows: air-air (A-A: 0–0 ppm), air-low (A-L: 0–100 ppm), air-high (A-H: 0–1,000 ppm), low-air (L-A: 100–0 ppm), low-low (L-L: 100–100 ppm), high-air (H-A: 1,000–0 ppm) and high-high (H-H: 1,000–1,000 ppm). Food consumption was measured for a 2-day period before exposure, 3 times a week during the pre-gestational exposure period and at 2–3-day intervals throughout the gestational exposures. Rats were weighed before exposures, and on exposure days 1, 5, 9, 13, Gd 17, and prior to sacrifice on Gd 21. Necropsies were performed on all animals and organs (liver, lung, spleen and kidneys) were weighed. Histopathological examinations were performed on tissues (ovaries, uterus, liver, lungs with trachea, and kidneys) from 25% of the animals selected at random. Litters were examined for the presence of external, visceral and skeletal abnormalities as well as incidence of growth retardation and intrauterine mortality.

Effects noted in study and corresponding doses:

96–97 ppm = No adverse effects on relative liver, kidney, or spleen weight, or developmental indices (NOAEL); no adverse effect on relative lung weight, body weight, food consumption, or reproductive indices.

959–985 ppm = No adverse effects on relative lung weight, body weight, food consumption, or reproductive indices (NOAEL); increased relative liver, kidney, and spleen weight, increased incidence of skeletal anomalies including supernumerary ribs (Less Serious LOAEL).

Dose end point used for MRL derivation:

[X] NOAEL [ ] LOAEL 97 ppm for no effect on developmental indices (skeletal anomalies)
Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

Was a conversion used from intermittent to continuous exposure?
If so, explain: No adjustment for intermittent exposure was made because the pharmacokinetics of ethylbenzene indicate that the effects are most likely concentration-dependent and not duration-dependent.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

The human equivalent dose (HEC) was calculated using Formula 4-48 (page 4-60), from Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, EPA 1994f. The recommended equation is that for category 3 gases:

$$NOAEL_{[HEC]}\ (ppm) = NOAEL_{[ADJ]}\ (ppm) \times \frac{(H_{b/g})_A}{(H_{b/g})_H}$$

$$= 97\ ppm \times [1] = 97\ ppm$$

where,

Hb/g = blood/gas partition coefficient [the value of 1.0 is used for the ratio of $(Hb/g)_A/Hb/g)_H$ or if these partition coefficient values are unknown]
A, H = the subscripts A and H refer to animal and human, respectively.

The MRL for intermediate-duration inhalation exposure to ethyl benzene is calculated, using the $NOAEL_{[HEC]}$ and a sum uncertainty factor of 100 (10 for extrapolation from animals to humans, 10 for human variability):

$$MRL = \frac{NOAEL_{[HEC]}}{UF}$$

or,

$$MRL = \frac{97\ ppm}{100} = 0.97 = 1.0\ ppm$$

Other additional studies or pertinent information that lend support to this MRL: The NOAEL of approximately 100 ppm is supported by other studies. In Fischer 344/N rats, administration of 99.4 ppm ethylbenzene for 13 weeks produced no effect on absolute and relative lung or liver weight; administration of 246 ppm for the same duration caused increases in these parameters (NTP 1992). In a companion study by Andrew et al. (198 l), rabbits exposed to ethylbenzene using the same paradigm showed no effect on relative liver weight at 99 ppm, but increased absolute and relative liver weight at 962 ppm. The choice of the NOAEL of approximately 100 ppm observed in Andrew et al. (1981) is supported by other studies. In Fischer 344/N rats, administration of 99.4 ppm ethylbenzene for 13 weeks produced no effect on absolute and relative lung or liver weight; administration of 246 ppm for the same duration caused significant increases in these parameters (NTP 1992). In a companion study by Andrew et al. (1981), rabbits exposed to ethylbenzene using the same paradigm showed no effect on relative liver weight at 99 ppm, but increased absolute and relative liver weight at 962 ppm. Although deficient in experimental details, the studies reported by Ungvary and Tatrai (1985) support a NOAEL of approximately 100 ppm. In rats, exposure during gestation to ethylbenzene for 24 hours a day for 9 days at doses ranging from 138 to 552 ppm resulted in fetal resorption and retardation of skeletal development in surviving fetuses (Ungvary and Tatrai 1985). Increased incidence of extra ribs and anomalies of the urinary tract were observed at the 552 ppm dose level. No effects were observed after exposure to 138 ppm for 6 hours a day for 9 days (Ungvary and Tatrai 1985). Mice exposed to 115 ppm ethylbenzene during gestation demonstrated an increased incidence of anomalies of the urinary tract (Ungvary and Tatrai 1985). The nature of the renal malformation was not characterized, and no maternal toxicity was reported. In addition, reduction in the weight of female fetuses was reported in rabbits exposed to 115 ppm during gestation (Ungvary and Tatrai 1985). Cragg et al. (1989) observed sporadic salivation in Fischer 344 rats exposed to 99 ppm ethylbenzene for 4 weeks.

Agency Contact (Chemical Manager): Jessilyn Taylor

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to fiid specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2- 1, 2-2, and 2-3) and figures (2- 1 and 2-2) are used to summarize heahh effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequencv/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that, caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

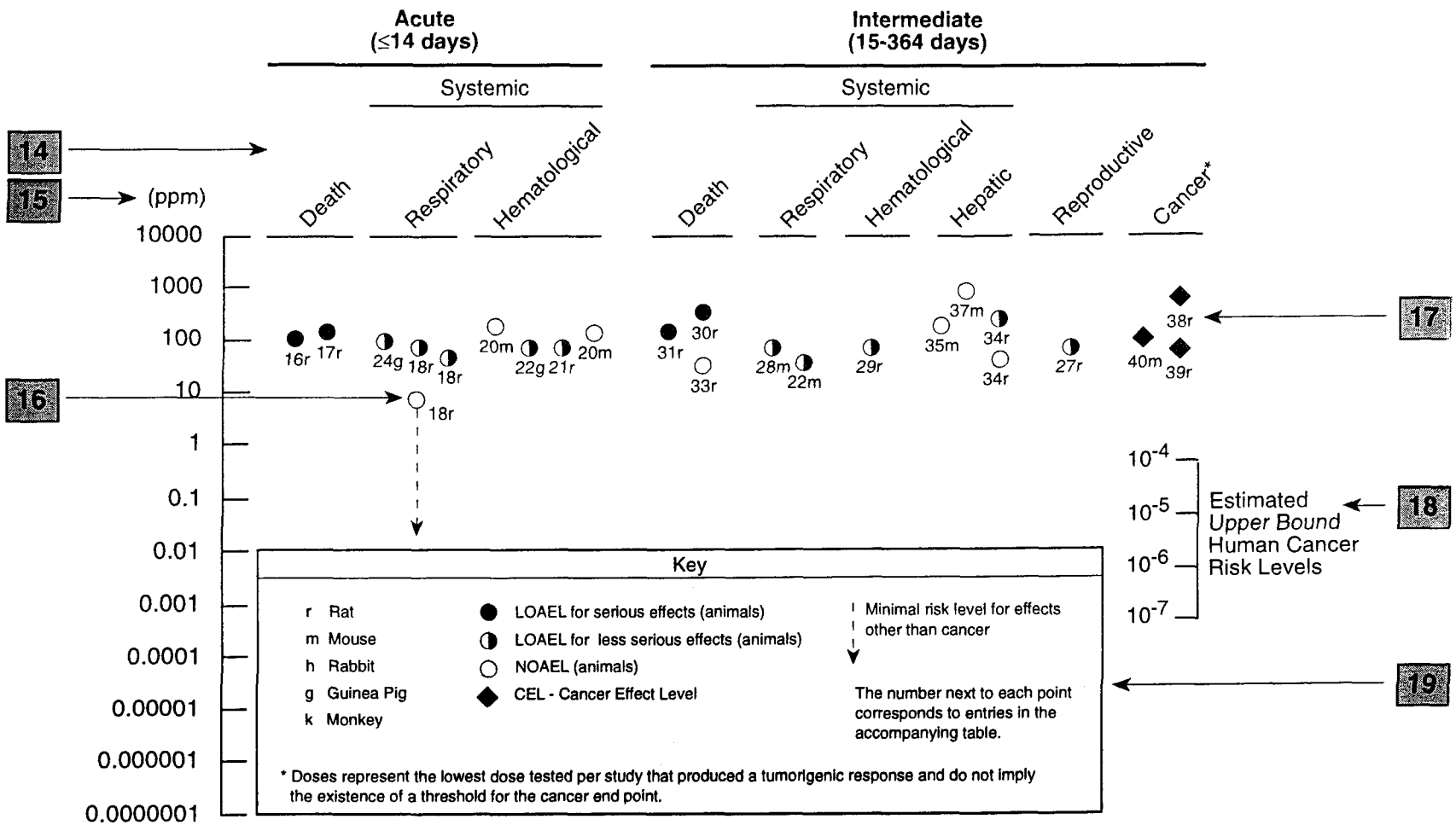
1 → TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10 ppm^3; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1 . What effects are known to occur in humans?

2 . What effects observed in animals are likely to be of concern to humans?

3 . What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In **vitro*** data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.8, “Interactions with Other Substances,” and 2.9, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors nsed in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOL

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level

ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie

APPENDIX C

MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short-term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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